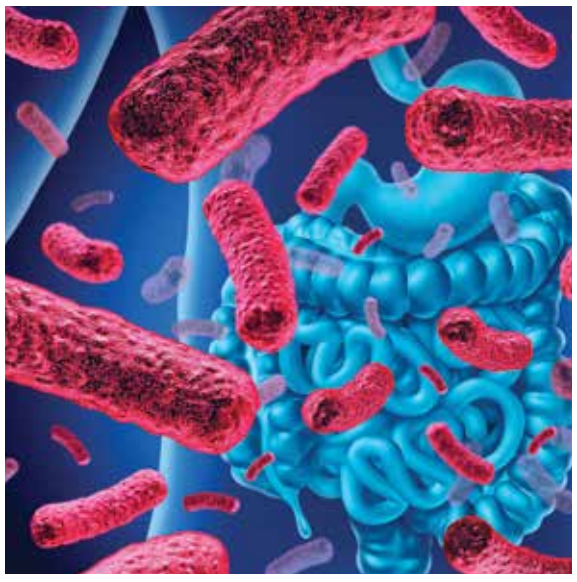
ASN
Kidney News
January 2019 | Vol. 11, Number 1

Study Points to Link between Gut Microbes and Posttransplantation Infections

By Bridget M. Kuehn



The mix of bacteria in the gut may predispose some kidney transplant patients to urinary tract infections, according to a study presented at Kidney Week 2018.

About one in five patients experience a urinary tract infection after kidney transplantation, said John Lee, MD, MS, a transplant nephrologist at New York Presbyterian Hospital—Weill Cornell Medical Center. These infections can usually be successfully treated with antibiotics, but in rare circumstances they can have serious consequences like graft loss and death, he noted. Finding ways to prevent such infections could help improve outcomes.

To examine how gut bacteria may contribute to the risk of urinary tract infection, Lee and his colleagues used DNA sequencing to assess the abundance of *Escherichia* and *Enterococcus* bacteria in fecal samples from 169 kidney transplant recipients during the 3 months after their transplantations. They found that 36 patients experienced urinary tract infections with Enterococcus species and 36 experienced urinary tract infections with Escherichia species during that period. Patients in whom these urinary tract infections developed were more likely to have a greater proportion of the corresponding bacteria in their gut, and the strain of bacteria in the urine was similar to that found in the gut, suggesting that the gut is likely the source of infection.

"Our data suggest people who have gut dysbiosis are at increased risk of developing urinary tract infections," Lee said. "People with recurrent urinary tract infections had the worst gut dysbiosis."

Nephrologist Dominic Raj, MD, professor of medicine, biochemistry, and genetics, and of biostatistics and epidemiology at George Washington University in Washington, DC, said it's not surprising that bacteria from the gut might be contributing to these infections, noting that it's "not uncommon for bacteria from stool to migrate to the urinary tract."

Lee cautioned that the findings are preliminary and must be confirmed, but if they are confirmed, it may suggest that modifying the gut microbiome could decrease the risk of urinary tract infections.

"If people with recurrent urinary tract infections have a gut dysbiosis that seems to predict urinary tract infections, then maybe you could use a prebiotic or probiotic approach to prevent that problem, rather than treat subsequent infections as they come up with a continued course of antibiotics," Lee explained.

He noted studies have found that fecal transplantation may help reduce urinary tract infections (1). But this field is evolving rapidly to test other targeted therapies, like giving patients beneficial bacteria (probiotics) or prebiotics, the

Continued on page 5

National Burden of CKD Is High—and Rising

Especially in Younger Adults, Trends Are "Moving in the Wrong Direction"

By Timothy O'Brien

Measures of the burden of chronic kidney disease (CKD) have risen dramatically in the 21st century—including more than 50% increases in rates of premature death and disability-adjusted life-years due to CKD. Those are among the alarming findings of a new analysis of changes in the health impact of CKD, published in late 2018 in *JAMA Network Open* (1).

The rising burden of CKD has occurred at a time when the United States has seen declining health burdens overall and from noncommunicable diseases in particular, according to the analysis of national and state-level data.

"Clearly, there needs to be more emphasis on prevention and addressing risk factors, but also on therapies to

Continued on page 3

Inside

Baxter
TrueVue **Analytics**
DIGITAL HEALTH SOLUTIONS

CRRT BUILT FOR **MY** ICU.

> The ability to look at the trends in our data has made a huge change in the way we provide therapy. The reporting with **TRUEVUE Analytics** has allowed us to really improve our goals and communication."
>
> — *Jillian, RN*

When Jillian Kouns decided to make a career change and become an ICU nurse 6 years ago, she was amazed to see the difference that CRRT with the PRISMAFLEX System could make for her patients. TRUEVUE Analytics software allows Jillian and her team to see the big picture and makes it that much easier to help her provide the best quality of care possible for these patients. Because at Baxter, supporting RNs like Jillian to deliver the best possible CRRT program is our priority.

Watch Jillian's story at
renalacute.com/stories

COMPLETE SUPPORT | PATIENT SAFETY | FLEXIBILITY

The PRISAFLEX Control Unit is intended for: Continuous Renal Replacement Therapy (CRRT) for patients weighing 20 kilograms or more with acute renal failure and/or fluid overload. Therapeutic Plasma Exchange (TPE) therapy for patients weighing 20 kilograms or more with diseases where fluid removal of plasma components is indicated.

Rx Only. For the safe and proper use of the devices mentioned herein, please refer to the appropriate Operator's Manual.

USMP/MG120/18-0006a(1) 1/19

National Burden of CKD

Continued from page 1

treat or reverse CKD," said senior author Ziyad Al-Aly, MD, of the Washington University School of Medicine in St. Louis and Veterans Affairs of St. Louis Health Care System. "Our report should be used to raise awareness of CKD among policymakers—unfortunately, it is often ignored—and CKD should be included in the public health agendas at the county, state, and federal levels. This report should be also used to advocate for more research funding in kidney disease, which in our view should be aligned with the burden of disease."

The study raises special concerns about the rising impact of CKD in younger Americans. "We expected to see that burden of CKD would rise as the US population aged," Al-Aly said. "But we were alarmed that the probability of death increased among those in the 20- to 54-year age group and that this increase was mostly driven by death due to diabetic CKD.

"Our findings suggest not only increased burden of CKD among this segment of the population, but that it was driven by increased exposure to metabolic and dietary risk factors and, most alarmingly, this has resulted in increased probability of death due to CKD among this young age group. Metabolic and dietary risks among this age group should be targeted aggressively to reduce burden of CKD."

Measures of CKD burden increase nationwide

The researchers analyzed 2002–2016 data from the Global Burden of Disease study (2). The baseline year corresponded to the introduction of the National Kidney Foundation's Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines; CKD was defined as an estimated glomerular filtration rate of under 60 mL/min/1.73 m^2. Al-Aly's coauthors were Benjamin Bowe, MPH, Yan Xie, MPH, Tingting Li, MD, Ali H. Mokdad, PhD, Hong Xian, PhD, Yan Yan, MD, PhD, and Geetha Maddukuri, MD.

The researchers analyzed estimates of CKD burden for all 50 states and Washington, DC. Trends in CKD mortality attributable to diabetes, hypertension, glomerulonephritis, and other causes were analyzed to obtain location-, sex-, age-, and year-specific estimates, along with estimates of nonfatal outcomes. The analyses used data and methods developed by the GBD collaborator network, including integrative metaregression methodology, an approach that integrates all available evidence to estimate the burden of CKD and other health conditions under the same computational framework.

"This allows us to compare the burden of kidney disease vis a vis the burden of other diseases," Al-Aly said. "You can think of it as a summary estimate of all that we know about the epidemiology of CKD in the United States over the past 15 years."

The study focused on four measures of CKD burden, all of which showed major changes from 2002 to 2016:

- *Deaths due to CKD* rose from 52,127 to 82,532, an increase of 58.3%. Nationwide, the rate of CKD deaths increased from 18 to 26 per 100,000 population, a 41.1% increase. Standardized for age, the rate of death from CKD rose from 14 to 16 per 100,000 population: a 17.9% increase.
- *Disability-adjusted life years (DALYs)* lost to CKD jumped from about 1.3 million to over 1.9 million: a 52.6% increase. Age-standardized DALY rates increased from 371 to 440 per 100,000 population, an increase of 18.6%.
- *Years living with disability (YLD)* due to CKD increased by 47.8% overall. The age-standardized YLD rate in 2016 was 170 per 100,000 population, for a 17.7% increase compared with 2002.
- *Years of life lost (YLL)* due to CKD exceeded 1.2 million years in 2016, representing a 55.6% increase. The age-standardized YLL rate was 270 per 100,000 population, a 19.3% increase.

Age-standardized death rates increased by 20.0% for CKD due to diabetes, 19.8% for hypertension, 11.1% for glomerulonephritis, and 11.0% for other causes. For age-standardized DALYs, rates were 21.8% for diabetes, 22.0% for hypertension, 10.4% for glomerulonephritis, and 10.3% for other causes. The age-standardized YLD rate for CKD due to diabetes was 61.8%.

Significant variation by state

While the increase in CKD burden was observed nationwide, there were substantial variations between states. The states with the highest age-standardized DALY rates were Mississippi, Louisiana, and Alabama: 697, 681, and 604 DALYs per 100,000 population, respectively. The states with the lowest rates were Vermont, Washington, and Colorado: 321, 328, and 331 DALYs per 100,000.

The magnitude of the increase in DALYs due to CKD was greatest in Oklahoma, 32.9%; West Virginia, 31.3%; and Texas, 30.9%. The states with the least increase in age-standardized DALYs were Nevada, 6.3%; New Jersey, 6.8%; and Massachusetts, 8.8%. The researchers note that the states with greater increases in CKD also have the highest adult obesity rates.

Deaths from CKD also varied widely among the states: the age-standardized death rate was more than twice as high in Louisiana compared to Vermont (28 versus 11 per 100,000 population). The largest changes in age-standardized CKD death rate were seen in Iowa, 41.0%; Washington, 38.1%; and Idaho, 34.6%. The smallest changes were in Nevada, –2.8%; New Jersey, 2.9%; and Massachusetts, 5.4%.

Decomposition analyses were performed to explore possible explanatory factors. Of the national increase in DALYs, 40.3% was due to increased risk exposure, 32.3% to aging, and 27.4% to population growth. Metabolic risk factors accounted for 93.8% of the overall change in age-standardized CKD DALY rates. The main contributors were:

- High fasting plasma glucose: a 29.5% change from 2002 to 2016 was linked to a 9.3% increase in age-standardized DALYs.
- High body mass index: a 30.9% change contributed to a 6.2% increase in DALYs.
- High systolic blood pressure: a 10.1% change resulted in a 2.3% increase in DALYs.
- Dietary risks—especially high intake of sodium and sugar-sweetened beverages—contributed to 5.3% of the change in age-standardized CKD DALY rates.

Diabetes and high blood pressure were the major factors associated with CKD-related disability. A 21.8% increase in CKD due to diabetes contributed to an 11.8% increase in age-standardized DALY rates nationwide, while a 22.0% increase in CKD due to hypertension led to a 4.0% increase in DALYs. Glomerulonephritis and other causes of CKD led to 1.1% and 1.7% increases in DALYs, respectively.

Special concern about CKD trends before age 55

The absolute probability of death due to CKD in younger adults (20 to 54 years) remained small, increasing 0.099% in 2002 to 0.125% in 2016. However, this represented a substantial increase of 26.8%. In this age group, 69.1% of the increased probability of death due to CKD was attributable to diabetes. Mississippi, Louisiana, and Alabama had the largest increases in probability of death due to CKD in younger adults.

In older adults aged 55 to 89, the probability of death due to CKD rose from 1.95% to 2.45%, for an increase of 25.6%. Diabetes accounted for 34.8% of the increase and a lower probability of death from competing causes for 37.2%.

As measured by the sociodemographic index (SDI), a standardized composite measurement used in the Global Burden of Disease study, sociodemographic development in the United States increased from 2002 to 2016. The increase in SDI was accompanied by a decrease in age-standardized DALY rates from all causes and from noncommunicable diseases.

But CKD was the exception. "Chronic kidney disease diverged from this trend in that as SDI increased, age-standardized DALY rate of CKD increased," Al-Aly and colleagues write. With the change in sociodemographic development, age-standardized CKD DALY rates increased in all states; the sole exception was Washington, DC. The burden of CKD nationwide and at the state level increased despite significant decreases in communicable, maternal, neonatal, and nutritional diseases, as well as noncommunicable diseases.

Of special concern is the rising probability of death due to CKD in younger adults, with diabetes being by far the greatest contributor. The rising burden of CKD in this age group has serious consequences not just for health and well-being, but also for the economy.

"If CKD is developing earlier in life, it's affecting the part of the population that contributes most to economic prosperity and human capital," said Al-Aly. "And since these patients have more years to live, the costs to the healthcare system and the burden to themselves [are] going to be huge."

The authors note that the increasing burden of CKD is "antithetical" to the declines in all-cause and noncommunicable disease burden, tied to increased sociodemographic development. "This finding may reflect the degree to which progress has been made in addressing the burden of cardiovascular disease (which shares several risk factors with CKD) and the relative stagnation in progress in addressing the burden of CKD," Al-Aly and colleagues write. Sociodemographic progress may be associated with increased exposure to dietary risk factors and "more pronounced expression of metabolic risk factors," such as obesity and diabetes.

From a clinical standpoint, the findings highlight the need for continued efforts to reduce lifestyle risks. "The focus should be on reducing risk exposure including metabolic and dietary risks among young adults," Al-Aly noted. "We expect things to improve with time, but for CKD the story is remarkably different—we are doing worse now than we did 15 years ago, and this should not be acceptable."

He called for concerted efforts regarding CKD risk factors at the state and national policy levels, with efforts to address factors contributing to the increase in CKD. "For example, we know that availability of calorie-dense foods and sugar-sweetened beverages [is] driving up obesity rates and diabetes," he said. "Policy interventions should be devised to steer people away from these—policy tools could include taxes, and incentives for more healthful options. Equally important is to address the issue with the food and beverage industries." He cited the US ban on trans fats as a successful example.

The findings also have implications for action by ASN and other specialty and professional groups, according to Al-Aly. "I think there needs to be a realization that this train is moving really fast and urgent attention is needed to deal with it today, and to prepare the nation to address the consequences of this epidemic in tomorrow's world." ■

References

1. Bowe B, et al. Changes in the US burden of chronic kidney disease from 2002 to 2016: An analysis of the Global Burden of Disease Study. *JAMA Netw Open.* 2018; 1(7):e184412. doi:10.1001/jamanetworkopen.2018.4412
2. www.healthdata.org/gbd

ASN KidneyNews

ASN Kidney News is published by the American Society of Nephrology
1510 H Street NW, Suite 800, 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 1510 H Street NW, Suite 800, 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, 1510 H Street NW #800, 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.

ASN Corporate Supporters

ASN gratefully acknowledges the Society's Diamond and Platinum Corporate Supporters for their contributions in 2018.

Diamond Level

AstraZeneca

FRESENIUS MEDICAL CARE

Otsuka

relypsa
A Vifor Pharma Group Company

Platinum Level

AMGEN

KERYX BIOPHARMACEUTICALS, INC

REATA PHARMACEUTICALS

Reasserting the Value of Nephrology

By David L. White

Nephrology faces challenges. Clinically, other internal medicine specialties increasingly are managing diseases traditionally considered in the domain of the nephrologist. Funding for kidney research is less per patient than every other major disease, such as cancer, cardiovascular disease, and diabetes. And the next generation is less interested in nephrology careers than any previous generation.

The American Society of Nephrology (ASN) is committed to working with every member of the kidney community—particularly the society's more than 20,000 members—to overcome these challenges, assert the value of nephrology, and articulate a positive, bold vision for the specialty's future. The question is no longer should ASN attempt to accomplish these goals, but how.

The current ASN Strategic Plan is in its third year, and the ASN leadership and staff are focused on the plan's fifth goal to "Assert the value of nephrology to health and science professionals, health care systems, and other stakeholders to ensure high-quality care for patients" by:

- Defining the scope of nephrology practice and articulating a vision for nephrology in the future.
- Facilitating improvements in kidney care, research, and education by using all available data sources to produce recurring reports about the state of nephrology.
- Demonstrating that the specialty of nephrology adds unique value to health care delivery that results in better outcomes for the millions of people with kidney diseases.

By conducting research, evaluating current trends in nephrology and other specialties, and studying the approaches peer societies have employed to increase interest in their specialty, ASN is beginning to finalize a strategy to assert the value of nephrology. During the last two years, ASN has interviewed leaders in medicine, both in nephrology and other specialties, the society's members, and representatives from peer societies.

The ASN leadership met twice during summer 2018 to distill these insights, ideas, and suggestions into an action plan. These sessions resulted in a draft outline that was reviewed during the fall by each of ASN's eight mission-based committees:

1. Career Advancement Committee
2. Continuous Professional Development Committee
3. Diversity and Inclusion Committee
4. Media and Communications Committee
5. Policy and Advocacy Committee
6. Publications Committee
7. Quality Committee
8. Workforce and Training Committee

To incorporate considerable feedback from the committees, ASN leaders and staff revised the draft outline and presented it in several forums at ASN Kidney Week 2018, including the joint meeting between the division chiefs and nephrology fellowship training program directors. Several thematic questions emerged during these productive discussions, including what is core to nephrology, should nephrologists further specialize, and what is best for people with kidney diseases?

Entering 2019 and the fourth year of its five-year strategic plan (2016–2020), ASN has identified several levers available to the society and the rest of the kidney community to execute a positive, bold vision for the future of nephrology, such as:

1. Delivering the message: Time to cure kidney diseases.
2. Fostering innovation and therapeutic developments.
3. Reinvigorating the educational continuum for nephrologists, particularly fellowship training.
4. Aligning certification and recertification (assessing lifelong competence) with the specialty.
5. Outlining the financial case to demonstrate that nephrologists add value to health systems.
6. Cultivating strong leaders.
7. Encouraging work-life balance and controlling burnout.
8. Advocating for greater reimbursement.

To finalize a plan for achieving the fifth goal of its strategic plan, ASN is simultaneously building upon the continued success of its ongoing initiatives such as Kidney Week, the ASN Foundation for Kidney Research, the Kidney Health Initiative (KHI), Nephrologists Transforming Dialysis Safety (NTDS), KidneyX, *JASN*, and *CJASN*. ASN is also continuing to focus on increasing interest in nephrology careers via programs like Kidney STARS as well as addressing policy and advocacy issues that affect nephrologists and their patients.

Later this year, ASN will invite the society's members and the broader kidney community to comment on a draft version of the plan for reasserting the value of nephrology. In the meantime, please contact ASN Policy and Advocacy Specialist David L. White at dwhite@asn-online.org, if you would like to suggest ways ASN can be of most value to you.

Posttransplant Infections

Continued from page 1

types of fiber needed to feed beneficial bacteria in the gut. Raj noted a study in *Nature* that found giving neonates both lactobacilli and prebiotics reduced sepsis by one-third (2).

Lee noted the importance of members of the collaborative effort to conduct this project: Manikkam Suthanthiran, MD, from Weill Cornell Medicine; Eric Pamer, MD, from Memorial Sloan Kettering Cancer Center; and Iwijn De Vlaminck, PhD, from Cornell University. Testing whether such gut-targeted approaches might be useful in preventing or treating urinary tract infections is the next step for this research, if the results are verified, Lee said.

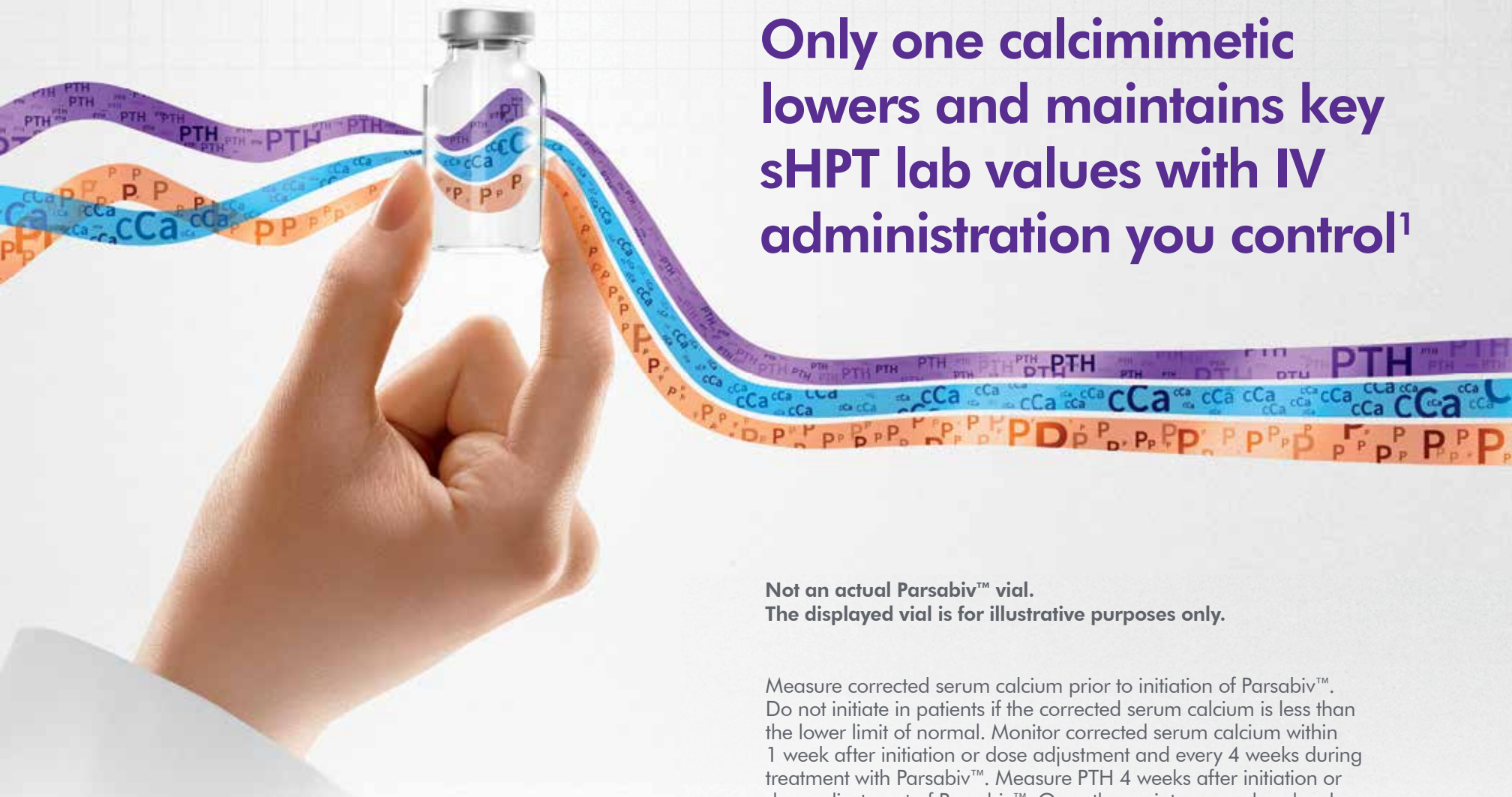
In addition to aiding research on the role of gut microbes in kidney disease and infection, Raj predicts that DNA sequencing of bacteria will eventually change the way clinicians diagnose infections.

"We are not going to wait for the culture to come," Raj said. "We are going to rely on DNA testing to identify the bacteria."

References

1. Raseen T, et al. Fecal microbiota transplantation for recurrent *Clostridium difficile* infection reduces recurrent urinary tract infection frequency. *Clin Infect Dis* 65; 10:1745–1747.
2. Pinaki P, et al. A randomized synbiotic trial to prevent sepsis among infants in rural India. *Nature* 2017; 548: 407–412.

Gut Microbiota Dysbiosis Is a Novel Risk Factor for Urinary Tract Infections in Kidney Transplant Recipients. Kidney Week 2018 Oral Abstract 007.



Only one calcimimetic lowers and maintains key sHPT lab values with IV administration you control[1]

Not an actual Parsabiv™ vial.
The displayed vial is for illustrative purposes only.

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

Contraindication: Parsabiv™ is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including pruritic rash, urticaria, and face edema, 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.

IV = intravenous; sHPT = secondary hyperparathyroidism; PTH = parathyroid hormone; P = phosphate; cCa = corrected calcium.

Reference: 1. Parsabiv™ (etelcalcetide) prescribing information, Amgen.

Parsabiv™ (etelcalcetide) Injection for intravenous use

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

Visit **ParsabivHCP.com** for more information.

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 pruritic rash, urticaria, and face edema, have occurred with PARSABIV *[see Adverse Reactions (6.1) 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.

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.

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.

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. If formation of anti-etelcalcetide binding antibodies with a clinically significant effect is suspected, contact Amgen at 1-800-77-AMGEN (1-800-772-6436) to discuss antibody testing.

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/

Considerations in Chronic Kidney Disease and Transplantation

By Moro Salifu and Susanne B. Nicholas

Despite advances in the management of hypertension and diabetes—the two risk factors accounting for over 70% of all cases of chronic kidney disease (CKD)—the prevalence of CKD in the general population has risen from about 10% two decades ago to 14.8% in 2017, surpassing that of diabetes (9.4%) (1) and making it a major public health problem in the United States.

Minority populations disproportionately have hypertension and diabetes and consequently bear a disproportionate burden of CKD (2). This trajectory is unacceptable and requires heightened awareness, particularly among primary care providers and nephrologists, with the goal of reducing these disparities and the associated morbidity, mortality, and economic costs. Here, we outline the health disparities considerations in addressing patients with CKD and CKD risk factors.

Disparities in the burden of CKD

The National Kidney Foundation of the United States is credited for defining CKD as kidney damage lasting over 3 months with or without decreased estimated GFR (eGFR), evidenced by pathologic abnormalities, or an absolute eGFR less than 60 mL/min per 1.73 m^2 lasting over 3 months (3, 4). On the basis of this definition, guidelines were developed in 2002 that classify CKD into five stages, from kidney disease with preserved GFR to end-stage kidney failure. In stage 1, there is evidence of kidney damage, but GFR is preserved (>90 mL/min). Stage 2 is mild kidney damage with GFR 60 to 90 mL/min, stage 3 is moderate kidney damage with GFR 30 to 59 mL/min, stage 4 is severe kidney damage with GFR 15 to 29 mL/min, and stage 5 is end-stage kidney damage with GFR <15 mL/min. Patients in stage 5 are often treated with dialysis or kidney transplantation.

CKD is a public health problem (5). In the United States alone, 14.8% of the population, or over 48 million people, are afflicted with CKD. Yet, many patients do not know they have CKD. According to data from the Behavioral Risk Factors Surveillance System, the prevalence of self-reported CKD is very low in the U.S. general population. Reports range from 1.8% in Virginia to 4.0% in Arizona. Given the overall prevalence of CKD in the U.S. population of about 14.8%, these numbers mean that most patients with CKD are not aware they actually have it. Furthermore, data from the National Health and Nutrition Examination Survey show that the prevalence of CKD is highest in African Americans (16.9%), although they make up only 12% of the U.S. population, followed by non-Hispanic white (15.2%) and Hispanic (12.8%) individuals (6).

Cardiovascular disease is the leading cause of death in this population, and most patients die during the course of CKD before dialysis is indicated. In a study by Keith et al. (7), the 5-year mortality rates for CKD stages 2, 3, and 4 were 19.5%, 24.3%, and 45.7%, respectively, whereas the corresponding rates in patients in these stages who progressed to ESRD were much lower at 1.1%, 1.3%, and 19.9%. Cardiovascular events such as ischemic heart disease, heart failure, stroke, and peripheral arterial disease have also been demonstrated to increase with decreasing eGFR (8–11), calling into action greater awareness of the impact of CKD on cardiovascular disease morbidity and mortality.

The healthcare expenditure associated with CKD is enormous. In 2015, Medicare spent 11%, or $64 billion, for CKD, and 5.8%, or $34 billion, for ESRD, for a total of $98 billion. This does not include spending in the public sector, nor spending attributable to lost productivity. Spending for CKD patients 65 years old and older exceeded $55 billion, representing 20% of all Medicare spending in this age group, with over half of these expenses being devoted to patients with diabetes mellitus or heart failure. African Americans with CKD account for higher spending in all disease categories than do other racial groups (12). This disparity in spending also needs to be addressed. Opportunities for cost containment could be achieved through screening and early detection that particularly targets African Americans to modify risk factors, retard disease progression, and manage comorbidities (13).

Acknowledgment: This work is supported by the National Institute of Minority Health and Health Disparities (NIMHD) Grant # S21 MD012474 to the Brooklyn Health Disparities Center.

References

1. American Diabetes Association. Statistics about diabetes. Available at: http://www.diabetes.org/diabetes-basics/statistics/.
2. Kissmeyer L, et al. Community nephrology: Audit of screening for renal insufficiency in a high risk population. *Nephrol Dial Transplant* 1999; 14:2150–2155.
3. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis* 2002; 39:S1–S266.
4. Levey AS, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003; 139:137–147.
5. Levey AS, et al. Chronic kidney disease as a global public health problem: approaches and initiatives: A position statement from Kidney Disease Improving Global Outcomes. *Kidney Int* 2007; 72:247–259.
6. US Renal Data System. 2016 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2016. https://www.usrds.org/2017/download/v1_c01_GenPop_17.pdf.
7. Keith DS, et al. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 2004; 164:659–663.
8. Go AS, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; 351:1296–1305.
9. Hui X, et al. CKD and cardiovascular disease in the Atherosclerosis Risk in Communities (ARIC) study: Interactions with age, sex, and race. *Am J Kidney Dis* 2013; 62:691–702.
10. Chronic Kidney Disease Prognosis Consortium, Matsushita K, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: A collaborative meta-analysis. *Lancet* 2010; 375:2073–2081.
11. Bansal N. Evolution of cardiovascular disease during the transition to end-stage renal disease. *Semin Nephrol* 2017; 37:120–131.
12. US Renal Data System. 2016 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2016. https://www.usrds.org/2017/view/v1_06.aspx.
13. Harding K, et al. Current state and future trends to optimize the care of chronic kidney disease in African Americans. *Am J Nephrol* 2017; 46:176–186.

Moro Salifu, MD, is professor and chair of the department of medicine, SUNY Downstate Medical Center in Brooklyn, and Susanne B. Nicholas, MD, MPH, PhD, is associate professor of medicine in the divisions of nephrology and endocrinology, department of medicine, David Geffen School of Medicine at University of California.

Disparities in Identification of CKD

By Moro Salifu, Girish Nadkarni, Steven Coca, and Susanne B. Nicholas

Population-based screening and identification strategies for patients with CKD remain a challenge. Data from the Behavioral Risk Factors Surveillance System suggest that most patients with CKD do not know they have the condition. Screening strategies such as albuminuria and serum creatinine determinations are not widely used in the general population and are performed only on indication; hence, most patients with CKD go undetected, for several reasons.

First, although screening is indicated in patients with traditional risk factors for CKD, including diabetes, hypertension, older age, cardiovascular disease, history of acute kidney injury, and a family history of CKD, screening is generally not recommended in patients without risk factors (1). In comparison with whites (7.1%), the adjusted prevalence of diabetes is 12.6% in African Americans, 16.1% in Native Americans and Alaskan Natives, and 11.8% in Hispanics (2); therefore, minority populations should be targeted for CKD screening.

The prevalence of hypertension among non-Hispanic blacks (41.2%) is higher than that for non-Hispanic whites (28.0%) and Hispanic adults (25.9%); therefore, blacks/African Americans with a history of hypertension should specifically be targeted for CKD screening (3). Furthermore, hypertension awareness (85.7% vs. 82.7%) and treatment rates (77.4% vs. 76.7%) are higher, but hypertension control (49.5% vs. 53.9%) is lower in non-Hispanic blacks than in non-Hispanic whites, suggesting a higher risk for CKD in non-Hispanic blacks (4). Interestingly, these lower rates of blood pressure control are highly prevalent in non-Hispanic blacks, even with higher overall use of blood pressure–lowering medications, further highlighting the need to focus on increasing identification of CKD in particular racial and ethnic groups.

A second consideration regarding disparities in identification of CKD is that compared with individuals of European descent, African Americans have a threefold to fivefold greater risk of CKD, attributed in part to two African ancestral genetic variants (termed G1 and G2) of the *APOL1* gene on chromosome 22. Those with two risk alleles have been shown to have a sevenfold to 30-fold increased risk for the development of hypertension-related CKD and faster progression of CKD (5). It is estimated that approximately 36% of African Americans carry at least one *APOL1* G1 or G2 risk allele, and 14% carry two *APOL1* risk alleles (6). By contrast, G1 and G2 alleles are absent in people of European ancestry. The high allele frequency in the African American population has been attributed to evolutionary selection for their protective effect against infection by the parasitic trypanosome *Trypanosoma brucei rhodesiense*, which causes the most deadly form of African sleeping sickness. Despite this knowledge, no routine clinical testing is yet available for these gene variants as part of risk stratification for CKD in African American patients with hypertension.

Third, CKD is not part of any incentive-based payment model for primary care physicians (PCPs), and despite the benefits of early referral from primary care to nephrologists (7–9), PCPs recognize and recommend specialist care for progressive CKD less frequently than might be expected. The barriers identified for this discrepancy include lack of awareness of clinical practice guidelines and lack of clinical and administrative resources (10, 11).

There is an opportunity to define ways by which PCPs, through incentive-based payments, can have the needed administrative and clinical resources to enhance early referral of patients with CKD. Midlevel providers such as advanced practice nurses can enhance the ability of PCPs to be more efficient at detecting and referring patients early in their CKD trajectory (12). More of such midlevel resources are needed because even when the referral from a PCP to a nephrologist is optimal, we do not have sufficient numbers of nephrologists to manage the volume of referrals.

In the past decade, the number of internal medicine residents choosing nephrology for subspecialty training has progressively declined (13), worsening the already existing and growing shortage of nephrologists. Thus, there is a call to action for guidelines to better define comanagement strategies between PCPs and nephrologists (14). It is conceivable that such comanagement pathways may allow PCPs to provide evidence-based management to patients with CKD stages 1 to 3 (15), while reserving the treatment of patients with CKD stages 4 to 5 for nephrologists and other subspecialists (e.g., endocrinologists, cardiologists, and nutritionists). Shared decision-making has been explored for patients in advanced CKD stages to facilitate their choices for renal replacement therapy (RRT) and end-of-life care but has not been explored at the time of CKD diagnosis (16). Such an approach may likely promote patient engagement in self-care to participate in kidney health strategies.

Taken together, these three considerations constitute a major access issue in CKD. Patients are not identified early, they are not referred early, and there aren't sufficient numbers of nephrologists to handle the volume of CKD patients in the population. Consequently, minority populations carry the highest burden of delayed referral for CKD care, for a variety of reasons including those related to socioeconomic issues, communication barriers to patient education, and patient-related issues such as patients' beliefs, religious practices, and lack of trust in the healthcare system.

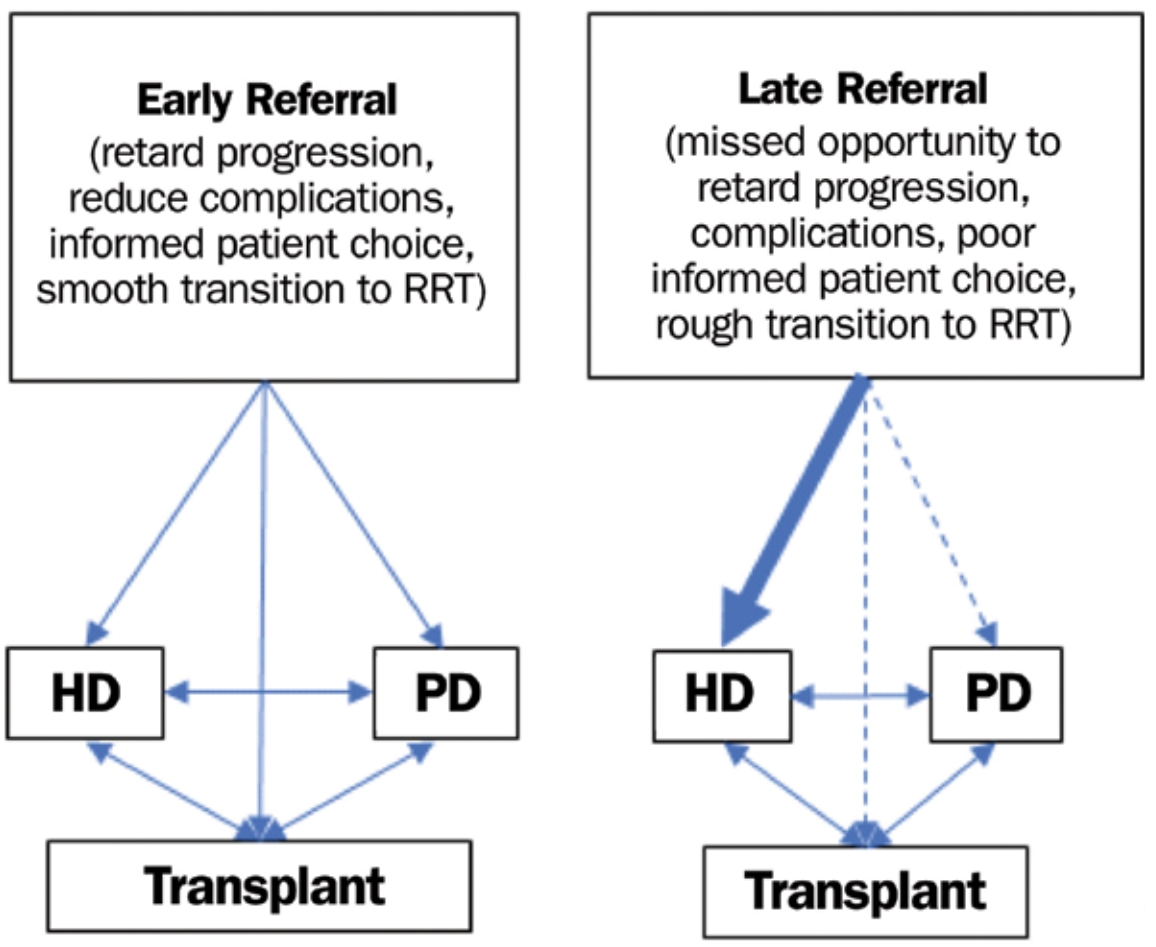
Physician bias in treating minority patients

Physician bias in treating minority patients also plays a role (17). Even among patients with health insurance, delayed referral to a nephrologist has been shown to be more likely in blacks, Hispanics, and older patients with CKD than in their white or younger counterparts (18, 19).

More recently, Koraishy et al. (20) showed that in a primary care setting, nephrology referrals were significantly more prevalent among patients with fast progression compared with slow progression. Even though a majority of patients with fast progression in the study were not referred, fast progression and being black were associated with increased odds of nephrology referral, suggesting that awareness of the high risk of CKD in black patients can improve the referral rates in this population. Figure 1 shows a model of early versus late referral in CKD. Early referral provides better patient treatment and better access to all forms of renal replacement therapy (RRT). Late referral results in worse outcomes and in most patients having undergone hemodialysis before they have access to peritoneal dialysis or transplantation as their choice of RRT.

Recent advances in informatics, data science, and molecular biomarkers may be a potential solution to these problems. Electronic medical records have been adopted nearly universally across health systems, and although they have certain limitations, they contain a multitude of longitudinal granular information. This information can be integrated with prognostic biomarkers that have high predictive value in early CKD (21) and genomic information (such as *APOL1* genotyping) (22) with the use of advanced data science techniques. Thus, comprehensive, multidimensional assessments of kidney risk in high-risk individuals (especially those with type 2 diabetes and those of African ancestry) can be generated and integrated with both the electronic medical record and care management tools, ensuring that appropriate care guidelines are being followed and tracked. Finally, large-scale analytics can be performed to quantify the population health impact of these measures, especially in vulnerable minority populations.

Figure 1. Model of early versus late referral in CKD



Early referral provides better patient management and better access to all forms of renal replacement therapy (RRT). Late referral results in worse outcomes and in most patients having to go through hemodialysis (HD, solid lines) before they have access to peritoneal dialysis (PD) or transplantation (dashed lines) as their choice of RRT.

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013; 3:1–150.
2. Golden SH, et al. Health disparities in endocrine disorders: biological, clinical, and nonclinical factors: An Endocrine Society scientific statement. *J Clin Endocrinol Metab* 2012; 97:E1579–E1639.
3. Yoon SS, Carroll MD, Fryar CD. Hypertension prevalence and control among adults: United States, 2011–2014. *NCHS Data Brief* 2015; 220:1–8.
4. Whelton PK, et al. Research needs to improve hypertension treatment and control in African Americans. *Hypertension* 2016; 68:1066–1072.
5. Genovese G, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science* 2010; 329:841–845.
6. Friedman DJ, Pollak MR. Genetics of kidney failure and the evolving story of APOL1. *J Clin Invest* 2011; 121:3367–3374.
7. Hansson L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: The Captopril Prevention Project (CAPPP) randomised trial. *Lancet* 1999; 353:611–616.
8. Cleveland DR, et al. Quality of prereferral care in patients with chronic renal insufficiency. *Am J Kidney Dis* 2002; 40:30–36.
9. Kinchen KS, et al. The timing of specialist evaluation in chronic kidney disease and mortality. *Ann Intern Med* 2002; 137:479–486.
10. Boulware LE, et al. Identification and referral of patients with progressive CKD: A national study. *Am J Kidney Dis* 2006; 48:192–204.
11. Junaid Nazar CM, et al. Barriers to the successful practice of chronic kidney diseases at the primary health care level: A systematic review. *J Renal Inj Prev* 2014; 3:61–67.
12. Thompson-Martin Y, McCullough PA, Agrawal V. Impact of an educational program for advanced practice nurses on Knowledge of Kidney Disease Outcomes Quality Initiative guidelines. *Nephrol Nurs J* 2015; 42:455–460, quiz 496.
13. Mallappallil M. Distracted by dialysis: Effects on nephrology fellowship and careers. *ASN Kidney News* 2018; 10:17–18.
14. Nissenson AR, et al. Opportunities for improving the care of patients with chronic renal insufficiency: Current practice patterns. *J Am Soc Nephrol* 2001; 12:1713–1720.
15. Ricardo AC, et al. Influence of nephrologist care on management and outcomes in adults with chronic kidney disease. *J Gen Intern Med* 2016; 31:22–29.
16. Murray MA, et al. Whose choice is it? Shared decision making in nephrology care. *Semin Dial* 2013; 26:169–174.
17. Institute of Medicine. Unequal treatment: What healthcare providers need to know about racial and ethnic disparities in health care, March 2002. https://www.nap.edu/resource/10260/disparities_providers.pdf.
18. Ifudu O, et al. Delayed referral of black, Hispanic, and older patients with chronic renal failure. *Am J Kidney Dis* 1999; 33:728–733.
19. Winkelmayer WC, et al. Determinants of delayed nephrologist referral in patients with chronic kidney disease. *Am J Kidney Dis* 2001; 38:1178–1184.
20. Koraishy FM, et al. Rate of renal function decline, race and referral to nephrology in a large cohort of primary care patients. *Fam Pract* 2017; 34:416–422.
21. Coca SG, et al. Plasma biomarkers and kidney function decline in early and established diabetic kidney disease. *J Am Soc Nephrol* 2017; 28:2786–2793.
22. Nadkarni GN, et al. Plasma biomarkers are associated with renal outcomes in individuals with *APOL1* risk variants. *Kidney Int* 2018; 93:1409–1416.

Moro Salifu, MD, is professor and chair of the department of medicine, SUNY Downstate Medical Center in Brooklyn; Girish Nadkarni, MD, is assistant professor of medicine and Steven Coca, DO, MS, is associate professor of medicine, division of nephrology, Mount Sinai School of Medicine in New York; and Susanne B. Nicholas, MD, MPH, PhD, is associate professor of medicine in the divisions of nephrology and endocrinology, department of medicine, David Geffen School of Medicine at the University of California.

Disparities in Risk Factors for Progression of CKD

By Moro Salifu and Susanne B. Nicholas

Many patients with CKD invariably experience progression, slow or fast, to later CKD stages and require renal replacement therapy at some point. Controlling the primary risk factors for CKD has been shown to slow progression of CKD but does not prevent the development of ESRD. The mechanisms underlying slow or fast progression of CKD are complex but are generally attributable to nephron loss from the primary disease, which sets a vicious circle of further nephron loss, characterized by hypertrophy and hyperfiltration of the remaining nephrons, intraglomerular hypertension, proteinuria, and toxicity of filtered proteins on tubular epithelial cells (1–3). Although these forces have been attributed to pertain to many glomerular diseases, the processes are particularly described in diabetic nephropathy, in which podocyte loss may be a downstream effect (4).

In addition, activation of the renin-angiotensinogen aldosterone system, development of metabolic acidosis, and, to a lesser extent, dyslipidemia and anemia further contribute to a progressive decline in renal function (5). Higher rates of CKD progression in African Americans than in other racial and ethnic groups may be accounted for by other progression-specific factors, such as the renin-angiotensinogen aldosterone system, BP (salt sensitivity), and response to injury. These factors have demonstrated marked racial disparities in physiology and in responses to treatment (6).

African Americans demonstrate lower plasma renin levels than do other racial groups (7, 8), which suggests that non–renin-mediated mechanisms play a major role in the pathogenesis of hypertension in this population. African Americans are more salt sensitive than are other racial groups (5), which results in greater amounts of salt and water retention, ultimately leading to plasma volume expansion and hypertension. This picture is further exacerbated by sympathetic overdrive in African Americans, largely resulting from socioeconomic stressors, which further drive hypertension (9).

Response to injury is also exacerbated in African Americans, as evidenced by overexpression of TGF-β1 in patients with hypertension and kidney disease (10). TGF-β induces fibrosis during the process of tissue repair and is a major mediator of glomerulosclerosis (11). It is also postulated that TGF-β1 modulates the expression of angiotensin II (12) and endothelin (13), further resulting in ischemia and injury to tissues. Taken together, TGF-β1 is overly expressed in African American patients with CKD and accelerates the progression of CKD in this patient population.

Differences in other risk factors for CKD and for CKD progression play important roles in the disparities associated with CKD. These risk factors may be divided into traditional and nontraditional risk factors. The traditional risk factors, such as diabetes, hypertension, history of acute kidney injury, malignancy, advancing age, cardiovascular disease, obesity, metabolic syndrome, and long-term use of nephrotoxic agents like nonsteroidal inflammatory drugs, are all well known and may be influential in any individual.

Nontraditional risk factors, such as poverty, lack of access to optimal healthcare, lack of health insurance, environmental factors, cultural beliefs, language and literacy barriers, and genetics, also described as social determinants of health, have been shown to play a greater role in ethnic minorities (14). In several instances, social conditions may have a direct effect on kidney disease and kidney disease progression. For example, it has been shown that reduced annual household income is associated with greater odds of both microalbuminuria and macroalbuminuria (15). Further, uninsured compared with insured individuals may be less likely to receive clinical care for optimal BP control (16), which may have a direct impact in CKD progression, particularly in African Americans.

Indeed, African Americans are susceptible to CKD progression not only from molecular and environmental factors but also from genetic factors. In one prospective study, Salifu et al. (17) showed that between African Americans and whites under equivalent glycemic control, there was no significant difference in diabetic CKD progression from one stage to the next, which suggests that other factors may explain the previously observed differences. *APOL1* high-risk variants are associated with greater risk of incident proteinuria and CKD in African Americans (18). In fact, the *APOL1* risk variants and interplay with environmental factors may account for up to 70% of the differences in the prevalence of kidney failure in African Americans compared with whites and individuals with nondiabetic kidney disease (19).

Continued on page 12 >

Progression of CKD

Continued from page 11

In this brief description of disparities in risk factors for progression in CKD, we have described some of the primary mechanisms that have been shown to generally lead to CKD and CKD progression. However, it is important to note the host of other risk factors that are typically not routinely considered when certain groups of patients are being evaluated for optimal care. This especially pertains to patients of racial and ethnic minorities, who are affected by many nontraditional risk factors that may directly or indirectly influence CKD and CKD progression. In addition to these nontraditional risk factors, there is a high prevalence of late referrals (30% to 40%) of patients in these minorities from primary care physicians to nephrologists (20). It is clear that early referral would optimize renal care before CKD begins and would potentially reduce CKD progression and prevent the need for dialysis. This practice should be encouraged.

References

1. Brenner BM. Nephron adaptation to renal injury or ablation. *Am J Physiol* 1985; 249:F324–F337.
2. Hostetter TH, et al. Hyperfiltration in remnant nephrons: A potentially adverse response to renal ablation. *J Am Soc Nephrol* 2001; 12:1315–1325.
3. Hostetter TH, Rennke HG, Brenner BM. The case for intrarenal hypertension in the initiation and progression of diabetic and other glomerulopathies. *Am J Med* 1982; 72:375–380.
4. Kriz W, Lemley KV. A potential role for mechanical forces in the detachment of podocytes and the progression of CKD. *J Am Soc Nephrol* 2015; 26:258–269.
5. Williams SF, et al. African Americans, hypertension and the renin angiotensin system. *W J Cardiol* 2014; 6:878–889.
6. Hsu CY, et al. Racial differences in the progression from chronic renal insufficiency to end-stage renal disease in the United States. *J Am Soc Nephrol* 2003; 14:2902–2907.
7. James PA, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; 311:507–520.
8. Materson BJ, et al. Single-drug therapy for hypertension in men: A comparison of six antihypertensive agents with placebo. The Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *N Engl J Med* 1993; 328:914–921.
9. Ely DL. Overview of dietary sodium effects on and interactions with cardiovascular and neuroendocrine functions. *Am J Clin Nutr* 1997; 65:594S–605S.
10. August P, et al. Transforming growth factor beta and excess burden of renal disease. *Trans Am Clin Climatol Assoc* 2009; 120:61–72.
11. Wang A, et al. Interference with TGF-beta signaling by Smad3-knockout in mice limits diabetic glomerulosclerosis without affecting albuminuria. *Am J Physiol Renal Physiol* 2007; 293:F1657–F1665.
12. Antonipillai I, et al. Transforming growth factor-beta is a renin secretagogue at picomolar concentrations. *Am J Physiol* 1993; 265:F537–F541.
13. Kurihara H, et al. Transforming growth factor-beta stimulates the expression of endothelin mRNA by vascular endothelial cells. *Biochem Biophys Res Commun* 1989; 159:1435–1440.
14. Harding K, et al. Current state and future trends to optimize the care of chronic kidney disease in African Americans. *Am J Nephrol* 2017; 46:176–186.
15. Crews DC, et al. Low income and albuminuria among REGARDS (Reasons for Geographic and Racial Differences in Stroke) study participants. *Am J Kidney Dis* 2012; 60:779–786.
16. Hall YN, et al. Characteristics of uninsured Americans with chronic kidney disease. *J Gen Intern Med* 2009; 24:917–922.
17. Salifu MO, et al. Effect of ethnicity on the progression of diabetic kidney disease independent of glycemic control. *Am J Nephrol* 2009; 30:261–267.
18. Chen TK, et al. APOL1 risk variants, incident proteinuria, and subsequent eGFR decline in blacks with hypertension-attributed CKD. *Clin J Am Soc Nephrol* 2017; 12:1771–1777.
19. Palmer ND, Freedman BI. APOL1 and progression of nondiabetic nephropathy. *J Am Soc Nephrol* 2013; 24:1344–1346.
20. Herget-Rosenthal S, et al. How does late nephrological co-management impact chronic kidney disease? An observational study. *Int J Clin Pract* 2010; 64:1784–1792.

Moro Salifu, MD, is professor and chair of the department of medicine, SUNY Downstate Medical Center in Brooklyn, and Susanne B. Nicholas, MD, MPH, PhD, is associate professor of medicine in the divisions of nephrology and endocrinology, department of medicine, David Geffen School of Medicine at the University of California.

Disparities in the Treatment of CKD and Efforts to Slow Progression

By Moro Salifu and Susanne B. Nicholas

The best chance to slow or reverse the progression of chronic kidney disease (CKD) is in CKD stage 1, when GFR is still preserved. The strategy in stage 1 CKD is to control comorbidities (treat to target) and to perform risk assessment and intervention for cardiovascular disease (1). Unfortunately, many patients, particularly those of minority extraction, do not get this early referral benefit, as noted in the previous section. Current evidence-based progression-specific treatment approaches in CKD include treating BP to acceptable goals, blockade of the renin-angiotensinogen aldosterone system (RAAS), and controlling metabolic acidosis. Trials of antioxidants by the use of bardoxolone, an inhibitor of oxidative stress that failed phase 3 clinical trials, was associated with worsened albuminuria and heart failure (2). Antagonists of inflammation, renal fibrosis, extracellular matrix deposition, and endothelin 1 have not yielded any meaningful clinical application. Interestingly, antagonists of the mineralocorticoid receptor have demonstrated reduced albuminuria but have been associated with high blood potassium levels, which may limit their use in patients with advanced CKD (3). Of the progression-specific treatment approaches, the RAAS system and BP control exhibit significant racial disparities, as detailed below.

There are no recommended different target BP levels based on race or ethnicity. The results from many randomized controlled trials addressing optimal BP in patients with CKD (4, 5) and observational studies (6–8) have yielded different results; nonetheless, guidelines issued by the Kidney Disease: Improving Global Outcomes (KDIGO), the European Society of Hypertension (ESH), and the European Society of Cardiology (ESC) and the Eighth Joint National Committee (JNC 8) cite evidence pointing to the benefit of lowering BP in individuals with CKD below the level acceptable in the general population; a BP goal below 140/90 mm Hg for those without albuminuria and 130/80 mm Hg for those with albuminuria (9–11). The Systolic Blood Pressure Intervention Trial (SPRINT) (12), which is the most recent of nondiabetic hypertension studies in which patients with CKD constituted 30% of the study population, provides additional evidence of the benefit of more intensive BP lowering to a systolic of pressure of 120 mm Hg or less, compared with a systolic pressure of 140 mm Hg or less, although the study was not powered to evaluate CKD per se. The benefit of BP lowering was similar between African Americans and whites.

The benefit of using inhibitors of the RAAS to achieve these optimal BP targets and to slow progression is well established in CKD (13–16). However, concerns have been raised about their effectiveness in African Americans. Unfortunately, only a few clinical studies have enrolled sufficient numbers of African Americans. A subgroup analysis of black patients in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (17) found less BP reduction with lisinopril than with amlodipine. This concern was addressed in a randomized controlled trial in the African American Study on Kidney Disease and Hyper-

tension (AASK) (18), which demonstrated that angiotensin-converting enzyme inhibitors appeared to be more effective than β-blockers or dihydropyridine calcium channel blockers in slowing GFR decline. The JNC 8 and other guidelines now recommend achieving a target BP below 140/90 mm Hg with a treatment strategy that also includes blockade of the RAAS, irrespective of race, unless not tolerated or contraindicated. Evidence suggests that angiotensin receptor blockers and angiotensin-converting enzyme inhibitors are equivalent in their effectiveness in retarding eGFR decline (19); hence, either class of drugs can be used to slow CKD progression, but the combination should be avoided because of the serious side effects, such as hyperkalemia and a greater decline in estimated GFR (20).

References

1. Levey AS, et al. National Kidney Foundation practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Ann Intern Med* 2003; 139:137–147.
2. Chin MP, et al. Risk factors for heart failure in patients with type 2 diabetes mellitus and stage 4 chronic kidney disease treated with bardoxolone methyl. *J Card Fail* 2014; 20:953–958.
3. Bakris GL, et al. Effect of finerenone on albuminuria in patients with diabetic nephropathy: A randomized clinical trial. *JAMA* 2015; 314:884–894.
4. Klahr S, et al. Modification of Diet in Renal Disease Study Group. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. *N Engl J Med* 1994; 330:877–884.
5. Lewis JB. Blood pressure control in chronic kidney disease: Is less really more? *J Am Soc Nephrol* 2010; 21:1086–1092.
6. Townsend RR. Blood pressure targets in CKD. *Adv Chronic Kidney Dis* 2015; 22:96–101.
7. Kovesdy CP, et al. Observational modeling of strict vs conventional blood pressure control in patients with chronic kidney disease. *JAMA Intern Med* 2014; 174:1442–1449.
8. Anderson AH, et al. Chronic Renal Insufficiency Cohort Study Investigators. Time-updated systolic blood pressure and the progression of chronic kidney disease: A cohort study. *Ann Intern Med* 2015; 162:258–265.
9. Taler SJ, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for management of blood pressure in CKD. *Am J Kidney Dis* 2013; 62:201–213.
10. Verbeke F, et al. A European Renal Best Practice (ERBP) position statement on the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for the management of blood pressure in non-dialysis-dependent chronic kidney disease: an endorsement with some caveats for real-life application. *Nephrol Dial Transplant* 2014; 29:490–496.
11. James PA, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; 311:507–520.
12. Wright JT Jr, et al. SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015; 373:2103–2116.
13. The Collaborative Study Group, Lewis EJ, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993; 329:1456–1462.
14. Ruggenenti PI, et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet* 1999; 354:359–364.
15. Brenner BM, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; 345:861–869.
16. Jafar TH, et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease: A meta-analysis of patient-level data. *Ann Intern Med* 2001; 135:73–87.
17. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; 288:2981–2997.
18. Wright JT Jr, et al. African American Study of Kidney Disease and Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: Results from the AASK trial. *JAMA* 2002; 288:2421–2431.
19. Barnett AH1, et al. Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 2004; 351:1952–1961.
20. Mann JF, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): A multicentre, randomised, double-blind, controlled trial. *Lancet* 2008; 372:547–553.

Moro Salifu, MD, is professor and chair of the department of medicine, SUNY Downstate Medical Center in Brooklyn, and Susanne B. Nicholas, MD, MPH, PhD, is associate professor of medicine in the divisions of nephrology and endocrinology, department of medicine, David Geffen School of Medicine at the University of California.

Disparities in Dialysis Modality Selection and Outcomes

By Subodh J. Saggi, Mary Mallappallil, and Moro Salifu

Smooth transition from CKD stage 5 to renal replacement therapy (RRT) remains a challenge. This transition period bears a high risk for mortality (1); hence, it requires a multidisciplinary pre-ESRD team approach (2) to address all aspects of care aimed at improving survival and providing adequate patient education about transplantation, in-center hemodialysis (HD), and home-based therapies (3).

Often dubbed an options clinic, this team-based approach needs to be conducted when RRT is anticipated within a year, sufficient time being allowed for access placement and transplant evaluation (4). The decision to choose a modality is not straightforward, and patients often go through states of change from thinking to acting, influenced by psychosocial, socioeconomic, religious, emotional, and systems issues and other factors. In one study, nearly half of patients did not decide on a modality despite receiving adequate education (5).

Poverty, lack of insurance, African American race, and Hispanic ethnicity are independently associated with a lower likelihood of pre-ESRD nephrology care (6, 7). The benefits of pre-ESRD nephrology care, including higher rates for arteriovenous fistula placement (8, 9), access to kidney transplantation (10), choice of peritoneal dialysis (PD) (7), and improved patient survival (11) are reduced in these populations. Furthermore, the benefits of access to care by a nephrologist before RRT to address CKD-specific complications, manage comorbidities, and educate patients about the options for RRT are reduced in these populations (12, 13). These observations plausibly explain the high rates of catheter use to start HD and the low rates of transplantation and PD in these populations.

On the basis of data from the United States Renal Data System, in 2015 the adjusted ESRD incidence rate ratios for African Americans, Hispanics, Asians, American Indians/Alaska Natives, and Native Hawaiians/Pacific Islanders, compared with whites, were 3.0, 1.3, 1.0, 1.2, and 8.4, respectively. The good news is that the excess risk of ESRD among minorities compared with whites over the past 15 years has declined (Figure 1). Most incident ESRD patients (87.3%) began RRT with HD, and 9.6% started with PD. As shown in Table 1, the percentage of African American incident ESRD patients who started with HD was slightly higher (91.1%) than for whites (87.3%) or Hispanics (89.3%). The rates were lower for PD in African Americans (8.1%) than in whites (9.9%) and Hispanics (9.1%) (14). These differences are not statistically different ($\chi 2$ 0.24; p = 0.9).

Interestingly, African American patients have better survival when using HD compared with whites in all age groups above 30 years. In the 18- to 30-year age group, there remains an increased mortality risk in non-Hispanic blacks versus non-Hispanic whites after adjustment for case mix (adjusted hazard ratio 1.19; 95% confidence interval 1.13–1.25) (15). Higher lean body mass is associated with a lower risk of mortality in HD patients, especially among non-Hispanic whites and African Americans (16). It can be postulated that the higher lean body mass observed in older African Americans at the initiation of dialysis withstands the catabolic state induced by uremia much longer and hence accounts for the better survival compared with other groups. However, no clear biologic mechanisms have been identified to explain these findings. Many investigators have looked at disparities in such factors as duration of dialysis treatments, achieved Kt/V, anemia management targets, lipid abnormalities, phosphorus levels, fibroblast growth factor 23 levels (17), nutritional profile, and different responses to inflammation (18), to explain the differences in survival. Levels of serum calcium, parathyroid hormone, and vitamin D have not been shown to be consistently associated with mortality.

It is also important to note that the size and location of a dialysis facility and the number of patients being treated can influence care and outcomes. In one study, facilities with 16 or more stations conferred a survival benefit. The association between increased mortality and facilities with 15 or fewer stations was stronger for racial minorities and for patients with diabetes or cardiovascular diseases. After adjustments, blacks had a 78% greater 1-year mortality risk in facilities with one to five stations, whereas whites had only a 26% greater risk (19). The authors explained that potential financial constraints faced by the small facilities may limit the opportunities for rigorous clinical care protocols and implementing measures for quality improvement. Consequently, small facilities may lack the experience to care for diabetic and cardiovascular patients and racial/ethnic minorities.

Figure 1. Improvement in the incidence ratios across minority groups over the past 15 years

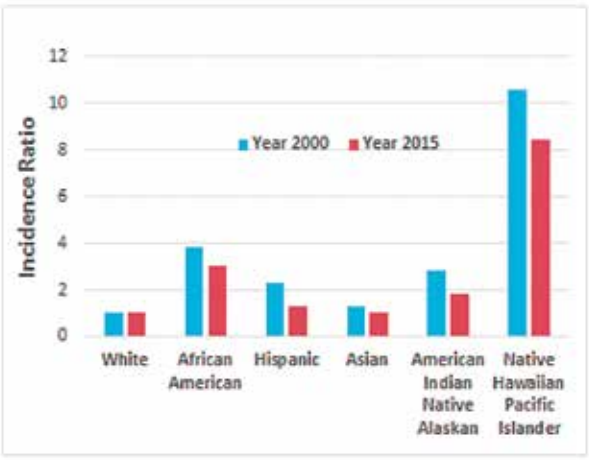


Table 1. Renal replacement therapy by race/ethnicity for incident dialysis patients in 2015

Race/ethnicity	HD (%)	PD (%)	Transplantation (%)
White (83.059)	87.5	9.9	2.8
Black (33.429)	91.1	8.1	0.8
Hispanic (18.151	89.3	9.1	1.7

Rates are similar for hemodialysis (HD) and peritoneal dialysis (PD) but significantly different for transplantation. African Americans are significantly less likely to undergo preemptive renal transplantation than are the other groups.

Reprinted with permission from USRDS, ADR 2017).

References

1. Sim JJ, et al. Disparities in early mortality among chronic kidney disease patients who transition to peritoneal dialysis and hemodialysis with and without catheters. *Int Urol Nephrol* 2018; 50:963–971.
2. Thanamayooran S, Rose C, Hirsch DJ. Effectiveness of a multidisciplinary kidney disease clinic in achieving treatment guideline targets. *Nephrol Dial Transplant* 2005; 20:2385–2393.
3. Manns BJ, et al. The impact of education on chronic kidney disease patients' plans to initiate dialysis with self-care dialysis: A randomized trial. *Kidney Int* 2005; 68:1777–1783.
4. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2012; 2:1–138
5. Hanko J, et al. Optimizing AVF creation prior to dialysis start: The role of predialysis renal replacement therapy choices. *Nephrol Dial Transplant* 2012; 27:4205–4210.
6. Nee R, et al. Impact of poverty and race on pre-end-stage renal disease care among dialysis patients in the United States. *Clin Kidney J* 2017; 10:55–61.
7. Gillespie BW, et al. Nephrology care prior to end-stage renal disease and outcomes among new ESRD patients in the USA. *Clin Kidney J* 2015; 8:772–780
8. Astor BC, et al. Timing of nephrologist referral and arteriovenous access use: The CHOICE Study. *Am J Kidney Dis* 2001; 38:494–501.
9. Ishani A, et al. Predialysis care and dialysis outcomes in hemodialysis patients with a functioning fistula. *Am J Nephrol* 2014; 39:238–247.
10. Winkelmayer WC, et al. Predialysis nephrologist care and access to kidney transplantation in the United States. *Am J Transplant* 2007; 7:872–879.
11. Singhal R, et al. Inadequate predialysis care and mortality after initiation of renal replacement therapy. *Kidney Int* 2014; 86:399–406.
12. Smart NA, Titus TT. Outcomes of early versus late nephrology referral in chronic kidney disease: A systematic review. *Am J Med* 2011; 124:1073–1080.
13. Prakash S, et al. Behavioral stage of change and dialysis decision-making. *Clin J Am Soc Nephrol* 2015; 10:197–204.
14. United States Renal Data System. 2016 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2016. https://www.usrds.org/2017/view/v2_01.aspx.
15. Yan G, et al. The relationship of age, race, and ethnicity with survival in dialysis patients. *Clin J Am Soc Nephrol* 2013; 8:953–961.
16. Wang J, et al. Lean body mass and survival in hemodialysis patients and the roles of race and ethnicity. *J Ren Nutr* 2016; 26:26–37.
17. Scialla JJ, et al. Race, mineral homeostasis and mortality in patients with end-stage renal disease on dialysis. *Am J Nephrol* 2015; 42:25–34.
18. Kalantar-Zadeh K, Norris KC. Is the malnutrition-inflammation complex the secret behind greater survival of African-American dialysis patients? *J Am Soc Nephrol* 2011; 22:2150–2152.
19. Yan G, et al. Facility size, race and ethnicity, and mortality for in-center hemodialysis. *J Am Soc Nephrol* 2013; 24:2062–2070.

Subodh J. Saggi, Mary Mallappallil, MD, and Moro Salifu, MD are affiliated with the Department of Medicine, SUNY Downstate Medical Center in Brooklyn.

Removing Disparities in Transplantation Referral and Outcomes: A Call to Action

By Moro O. Salifu, Amarpali Brar, Elena Zitzman, and Rahul M. Jindal

Kidney transplantation is the renal replacement therapy (RRT) of choice for most patients with ESRD because it is associated with improved survival and improved quality of life, and it is less expensive than dialysis. The process leading to transplantation is complex, with multiple necessary steps that must be completed before transplantation. Despite improvement in outcomes, disparity across the board in the transplantation process continues to be a major problem.

Barriers to cadaveric renal transplantation among blacks and women

Alexander and Sehgal (1) found that African Americans, women, and the financially disadvantaged have lower rates of completion of each step of the transplantation process required for listing and eventual transplantation, suggesting that many socioeconomic and other issues prevent this population from progressing in the transplantation process.

Survey results demonstrate that nephrologists consider preemptive transplantation to be the optimal treatment modality for eligible patients; however, late referral, health insurance status, and delayed evaluation by transplantation centers are perceived as major barriers to preemptive transplantation (2). Of the 95,456 patients on the waitlist in 2016, 36.4% were white and 33.2% were African American—a gap that has narrowed over the years (3). The rate of transplantation in patients on the waitlist continues to be higher in whites than in African Americans (4.0 vs. 2.8/100 patient years), largely because of a difference in the rates of living donor kidney transplantation (LDKT), which are higher in whites than in African Americans (1.5% vs. 0.4%).

Progress in reducing the disparity gap in deceased donor kidney transplantation

There is no significant difference in the rates of deceased donor kidney transplantation (DDKT) between whites and African Americans (2.4% vs. 2.5%) (4), in part because of changes in the allocation system and changing the date of waitlisting to the date of start of ESRD therapy (5, 6). Disparities in deceased organ donor rates have also disappeared because of significant increases in deceased organ donor rates in African Americans from 4 to 7.8 donors per 1000 deaths compared with whites (7.3 donors per 1000 deaths). The gap in graft survival at 5 years has also narrowed and is currently at 85% for whites and 82% for African Americans.

Racial disparities in renal allograft outcomes

Purnell et al. (7) found that the 5-year graft loss after DDKT improved from 51.4% to 30.6% for African Americans and from 37.3% to 25.0% for white adults who received a first-time renal transplant during 1990 to 2012. During the same time period, the 5-year allograft loss after LDKT improved from 37.4% to 22.2% for African Americans and from 20.8% to 13.9% for whites. Among LDKT recipients in the earliest cohort, African Americans were 53% more likely than whites to experience 5-year graft loss. There were no statistically significant differences in 1-year or 3-year graft loss after LDKT or DDKT in the most recent cohorts. Patient survival at 5 years after LDKT improved from 89.6% to 92.1% for whites and from 87.9% to 90.9% for African Americans, and patient survival at 5 years after DDKT improved from 78.8% to 81.2% for whites and from 79.9% to 84.2% for African Americans.

Using U.S. transplant registry data, Taber et al. (8) reported, in kidney recipients undergoing transplantation between 1990 and 2009, that the absolute risk difference between African Americans and whites for 5-year graft loss significantly declined over time (0.92% decrease per 5 years), whereas the relative risk difference significantly increased (3.4% increase per 5 years).

In the 2016 data from the United Network for Organ Sharing (UNOS) and the Organ Procurement and Transplantation Network (OPTN), 5-year living donor graft survival was lower for African American recipients than for any other racial or ethnic group, at 82.0% compared with 92.3% for Asian, 89.9% for Hispanic, and 85.7% for white recipients, respectively. Patient survival in living donor allografts did not show this trend (3). Higher immunologic risk resulting from HLA mismatches, higher panel reactive antibodies and genetic polymorphism in cytokine production, *APOL1* gene variants, lower bioavailability of calcineurin inhibitors associated with cytochrome P450 3A5 polymorphism, higher pretransplantation dialysis vintage, lower socioeconomic status income, reduced access to healthcare, and nonadherence have been suggested as possible reasons for inferior renal allograft outcomes (8–10). Overall, advances in immunosuppression and posttransplantation management may have helped improve these disparities in renal allograft outcomes.

The gender gap

Gender inequity in access to hemodialysis (HD) and kidney transplantation has created a public health crisis in the United States. Women have a lower chance of receiving HD and a kidney transplant than men, but they constitute the majority of living kidney donors (11). Kemph et al. (12) suggested that mothers might be more willing to donate, followed by fathers and siblings. Women are at a triple disadvantage: a reduced probability of receiving HD and hence being considered for transplantation; poorer access to transplantation by not completing a pretransplantation workup, moving up a waitlist and receiving a transplant; and higher sensitization to HLA antigens. Women also donated more living-related and unrelated kidneys but received fewer living kidneys than did men. Research is indicated to enable an understanding of the underlying societal gender bias in kidney transplantation (13).

The way forward

Despite several campaigns at the national level, disparity in living kidney transplants has not improved since 1995 (14). Recommendations from a consensus conference (15) to improve living kidney donation in minority populations included 1) removal of financial disincentives to living kidney donation; 2) implementing culturally tailored, community-based educational programming at multiple stages of the referral process; 3) engaging a transplant liaison in community nephrology practices and dialysis; and 4) developing a research strategy to better understand LDKT disparities and donor differences. Obviously, increasing awareness about these disparities and differences among community nephrologists, dialysis providers, and transplantation professionals is a critical first step toward improving the rates of LDKT in African Americans (16).

More importantly, addressing the social determinants of health at the population level is critical in reducing health disparities. In a recent study published in the *Clinical Journal of the American Society of Nephrology* (July 2018), Harhay et al. (17) used the UNOS/OPTN database to examine whether expanding Medicaid under the Affordable Care Act in the United States was associated with differences in the number of individuals who were preemptively waitlisted. The authors found that 24 states that fully implemented Medicaid expansion had a 59% relative increase in Medicaid-covered preemptive listings compared with an 8.8% relative increase among the 19 states that did not expand the program, with larger increases in Medicaid coverage among racial and ethnic minority listings than among white listings. This study clearly illustrates the potential to eliminate health disparities when social determinants of health such as health insurance coverage are addressed at the population level.

References

1. Alexander GC, Sehgal AR. Barriers to cadaveric renal transplantation among blacks, women, and the poor. *JAMA* 1998; 280:1148–1152.
2. Pradel FG, et al. A survey of nephrologists' views on preemptive transplantation. *Clin J Am Soc Nephrol* 2008; 3:1837–1845.
3. Hart A, et al. OPTN/SRTR 2016 Annual Data Report: Kidney. *Am J Transplant* 2018; 18:18–113.
4. US Renal Data System. 2016 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2016. https://www.usrds.org/2017/view/v2_06.aspx.
5. Hall EC, et al. Effect of eliminating priority points for HLA-B matching on racial disparities in kidney transplant rates. *Am J Kidney Dis* 2011; 58:813–816.
6. Stewart DE, et al. Changes in deceased donor kidney transplantation one year after KAS implementation. *Am J Transplant* 2016; 16:1834–1847.
7. Purnell TS, et al. Reduced racial disparity in kidney transplant outcomes in the United States from 1990 to 2012. *J Am Soc Nephrol* 2016; 27:2511–2518.
8. Taber DJ, et al. Twenty years of evolving trends in racial disparities for adult kidney transplant recipients. *Kidney Int* 2016; 90:878–887.
9. Freedman BI, et al. Apolipoprotein L1 gene variants in deceased organ donors are associated with renal allograft failure. *Am J Transplant* 2015; 15:1615–1622.
10. Taber DJ, et al. Outcome disparities between African Americans and Caucasians in contemporary kidney transplant recipients. *Am J Surg* 2017; 213:666–672.
11. Jindal RM, et al. Kidney transplantation and gender disparity. *Am J Nephrol* 2005; 25:474–483.
12. Kemph JP, et al. Kidney transplant and shifts in family dynamics. *Am J Psychiatry* 1969; 125:1485–1490.
13. Bloembergen WE, et al. Gender discrepancies in living related renal transplant donors and recipients. *J Am Soc Nephrol* 1996; 7:1139–1144.
14. Purnell TS, et al. Association of race and ethnicity with live donor kidney transplantation in the United States from 1995 to 2014. *JAMA* 2018; 319:49–61.
15. Rodrigue JR, et al. Living donor kidney transplantation: Best practices in live kidney donation: Recommendations from a consensus conference. *Clin J Am Soc Nephrol* 2015; 10:1656–1657.
16. Sajjad I, et al. The dynamics of recipient-donor relationships in living kidney transplantation. *Am J Kidney Dis* 2007; 50:834–854.
17. Harhay MN, et al. Association between Medicaid expansion under the Affordable Care Act and preemptive listings for kidney transplantation. *Clin J Am Soc Nephrol* 2018; 13:1069–1078.

Moro Salifu, MD, is a professor in and chair of the department of medicine, and Amarpali Brar, MD, is an assistant professor in the department of medicine, SUNY Downstate Medical Center in Brooklyn; Elena Zitzman, MD, is a research fellow, and Rahul M. Jindal, MD, PhD, MBA, is a professor in the department of surgery, Walter Reed, Uniformed Services University in Bethesda.

Mergers and Medicaid Expansion

By David White

In a fast-paced Kidney Week 2018 session titled "Reshaping Relationships and Transforming Care Delivery," Janis M. Orlowski, MD, MACP, chief health care officer of the Association of American Medical Colleges (AAMC), captured the dynamic environment of healthcare in the United States when she led the session with "Consolidation: Friend or Foe?"—the Christopher R. Blagg, MD, Lectureship in Renal Disease and Public Policy.

Orlowski captured the situation with a comparison of the 2008 merger of Mercy Hospital of Pittsburgh, a 160-year-old institution with 428 beds, with the University of Pittsburgh Medical Center, compared with the recent signed letter of intent to merge Baylor Scott & White Health and Memorial Herman, which had, respectively, 2017 operating revenues of $9.1 billion and $5.06 billion. The combined enterprise will have 68 hospital campuses, more than 1100 care delivery sites, about 14,000 independent and academic physicians, two health plans, and approximately 10 million patient encounters annually.

The year 2018 also saw the completion of the merger between Downers Grove–based Advocate Health Care and Wisconsin's Aurora Health Care, creating the 10th-largest not-for-profit hospital system in the country. The new combined system, called Advocate Aurora Health, has 27 hospitals, 70,000 employees, and about $11 billion in annual revenue. The merged system will keep dual headquarters in Illinois and Wisconsin. The $69 billion merger of CVS with Aetna should also be considered in this context.

Rural consequences

Some of the same factors driving these megamergers, along with the consequences of these types of mergers, have led to the closure of 80 rural hospitals since January 2010 and of 122 rural hospitals since January 2005.

Detailing the AAMC research in the "Future of Academic Medicines Series," Orlowski described three goals of the research as follows:

- How academic medicine is responding to a climate of increasing interinstitutional affiliation and system formation and growth,
- How strategies designed to create thriving and sustainable clinical enterprises affect academic medicine's clinical, educational, and research missions and what options can best assure the sustainability of all of these missions, and
- How academic medicine can bring value to nonacademic system partners.

The AAMC research pointed to several major factors driving trends:

- Proactive strategic vision,
- Market share,
- Population health, and
- Financial improvement and access to capital.

For market share, "the willingness to consider mergers, acquisition, and/or partnership activity may reflect a strategic plan by a teaching hospital to assemble a larger population base, cover a specific geographic area, achieve 'scale,' and reach a certain market share and/or target revenue," Orlowski said. She further noted that "there is a growing discussion as to whether benefits from merger, acquisition, and partnership (MAP) transactions can be attributed to 'consolidation' or 'scale' itself or whether the true variable associated with unlocking these benefits is 'integration'—particularly clinical integration." She also noted that whereas there is great potential for tackling the challenges of population health in these trends, it is also time for strong leadership on population health.

Some interesting factors in the movement to consolidation are within Medicare and Medicaid. Medicaid's platform has grown significantly in recent years, and the 2018 midterm elections mean that Idaho, Nebraska, and Utah will be the next three states to join Medicaid expansion. Medicare has seen some interesting changes as well, including the Medicare Shared Savings Program and accountable care organizations, which have grown from $316 million in payments in 2013 to $701 million in 2016, although many are waiting to see what effect the efforts of the Centers for Medicare & Medicaid Services to push these organizations into two-sided risk models will have. At the same time, Medicare private health plan enrollment grew to over 19 million beneficiaries, or 33% of all Medicare beneficiaries in 2017—up from a low of 5.3 million beneficiaries and 13% of all Medicare beneficiaries in 2004—based on a Medicare population of 56.9 million individuals.

Although in 2017, for the first time, the majority of first-year medical school matriculants were women, in nephrology there are still lags. Among active physicians, 28% of nephrologists are women, whereas 35% of physicians are female among all specialties. Among nephrology residents and fellows, 33% are female, whereas across all specialties, 46% are women. When all specialties are considered, 44% of physicians are age 55 or older, but in nephrology the corresponding figure is only 36%. Also, among the 44 largest specialties, the number of active physicians grew 9% overall, but in nephrology, it grew 19%.

Orlowski concluded that consolidation is not a trend—it's here now—and population health is moving

Figure 1. One-year mortality for patients starting dialysis under Medicaid expansion

in the direction of accountable care organizations. On the question of "economies of scale," she thinks the jury is still out.

Medicaid expansion and end stage renal disease

Amal Trivedi, MD, MPH, associate professor of health services, policy and practice, Brown School of Public Health, publicly released his study "The Affordable Care Act, Medicaid Expansion, and End-Stage Renal Disease" concurrently during his talk at the session and with the *Journal of the American Medical Association* nationally. Before the Affordable Care Act (ACA), one-fifth of nonelderly adults were uninsured at the time they began dialysis.

Trivedi presented that "among the broader population, there is an emerging body of evidence on the effects of Medicaid expansion:

- Gains in coverage,
- Improved access to care,
- Increased use of preventive services, and
- Better self-rated health.

The study aimed to measure the impact of ACA's Medicaid expansion on these factors:

- Insurance coverage at time of dialysis initiation,
- Predialysis nephrology care, and
- 1-year mortality for nonelderly patients with ESRD who begin dialysis.

The study used a quasiexperimental difference-in-differences analysis to examine the change in outcomes among new dialysis patients in Medicaid expansion states compared with nonexpansion states. It also included all patients in the United States aged 19 to 64 who began dialysis from the beginning of 2011 through the end of March 2017, excluding patients with Medicare coverage (including duals) and those with Veterans Administration (VA) coverage, inasmuch as the ACA coverage expansions would not apply to them, although they were included in a sensitivity analysis. This resulted in an analytic sample of over 236,000 patients.

Our primary outcome was all-cause mortality over the 1-year period that began with the 91st day after dialysis initiation," Trevidi said. "We used this definition of mortality because deaths among incident dialysis patients are not reliably reported within the first 90 days following dialysis initiation (this follows the United States Renal Data System approach). Additionally, only patients who initiated dialysis before January 1, 2016, were included for the mortality outcome to allow for follow-up (180,044 patients)."

The study also examined insurance coverage at the time of dialysis initiation, focusing on Medicaid coverage and being uninsured. It then looked at receipt of predialysis nephrology care. First, the study examined whether the patient had received care from a nephrologist before beginning dialysis and whether the patient had a fistula or graft during their first treatment session. The two nephrology care measures are tracked as part of the Healthy People 2020 goals for chronic kidney disease. The study used both statistical analyses and sensitivity analyses.

Figure 1 shows unadjusted 1-year mortality for patients beginning dialysis. Before expansion, mortality rates were nearly identical in expansion states (dashed black line) and nonexpansion states (solid red line). After expansion, the mortality rate in non-expansion states remained the same, but the mortality rate in expansion states declined after Medicaid expansion was enacted.

Trivedi concluded, "To sum up, the ACA's Medicaid expansion was associated with improved insurance coverage, access to care, and survival among nonelderly ESRD patients initiating dialysis. This supports the idea that the health effects of insurance coverage are likely greatest for patients with severe health conditions."

Caring for the Most Vulnerable Of Vulnerable Patients: **the Undocumented ESRD Population**

By Mukta Baweja

Immigration.

One of the most polarizing issues in the country was the topic of a special session devoted to Improving Care for Vulnerable Patients at ASN Kidney Week 2018. Speakers included Rajeev Raghavan, MD, FASN, associate professor of medicine/nephrology at Baylor College of Medicine; Valerie Luyckx, MD, Institute of Biomedical Ethics, Geneva, Switzerland; Lauren Stern, MD, assistant professor of medicine and nephrology at Boston University; and Jenny Shen, MD, assistant professor of medicine and nephrology at UCLA.

Understanding the issues surrounding the care of undocumented patients begins with numbers.

ESRD patients account for <1% of the Medicare population, yet they account for 7% of the Medicare budget, at a cost of $38 billion per year (2018). There are approximately 11 million undocumented immigrants in the United States. By a conservative estimate, 6500 of these undocumented immigrants suffer from ESRD (1) out of about 700,000 ESRD patients nationwide, so approximately 1% of our ESRD patients are undocumented.

And there is a geographic propensity as well: just 4 states account for about 50% of the undocumented population with ESRD: California (24%), Texas (14%), Florida (9%), and New York (8%). Of these 4 states, only 2—California and New York—offer chronic outpatient hemodialysis therapy using nonfederal funds as treatment options for the undocumented.

Although undocumented immigrants make up a small proportion of our patients, over 60% of nephrologists report that they have provided care to the undocumented and note rising prevalence, with most also reporting inadequate compensation that jeopardizes the long-term availability of treatment to the undocumented population (2).

Providing care to those without clear access to care is not without its burden. Understanding the social circumstances of a patient and the degree of their illness and suffering without sufficient means to help is an ethical and emotional dilemma. To quote Nathan Gray, MD, a palliative care physician and graphic narrator who recounts the patient experience: "I wish he'd had a better death, but more than that, I wish he'd had a better life." (3).

Our system isn't working. So what do we do to fix it? What are the next steps? We advocate. We educate. We demand a national policy for ESRD in the undocumented population.

Undocumented immigrants are more likely to be uninsured than legal immigrants and US citizens (4). And, since they are ineligible for federal services such as Medicare, full scope Medicaid, and the provisions under the Affordable Care Act, the only method for treatment is afforded under the Emergency Medical Treatment and Labor Act (EMTALA), or modified emergency Medicaid in some states, local funds, off-exchange insurance programs, and possibly third-party payers. Other states offer emergency-only dialysis, an extremely resource-intensive, expensive treatment with considerably higher mortality than standard hemodialysis.

Emergency dialysis

Emergency-only dialysis entails just that: dialysis only in cases of emergency after an ER visit, when there are significant symptoms or instability and hyperkalemia. Even without data, this practice already would presume to be associated with significant ethical and moral dilemmas. Consider a patient who is younger, a member of the workforce, and must tolerate the symptoms of end stage kidney disease until a near-death emergency permits them to receive treatment, only to then wait in the emergency room for several hours, perhaps while they have young children waiting for them at home. Then imagine them perhaps repeating the same sequence of events soon afterward.

One study showed that emergency dialysis costs $285,000 per patient per year, as opposed to chronic hemodialysis at $77,000 per patient per year (5) and is associated with a fivefold higher mortality after 3 years and a 14 times higher hazard ratio of death after 5 years (6). On top of this, studies of the patient experience are consistently clear that the practice of emergency-only dialysis can be emotionally devastating. Care that is provided by multiple and inconsistent healthcare providers, accumulation of symptoms to the point of distress, death anxiety, and family burden are all points of consideration for patients as well as for providers—who also are affected by the moral and ethical questions. Boston University's Stern said with regard to emergency-only dialysis, "As physicians we take an oath to do no

Continued on page 18

Undocumented ESRD Population

Continued from page 17

harm, and it really seems that we are doing harm with these practices."

Transplantation

Transplantation, which is excluded from EMTALA, has lower mortality, better quality of life, and is more cost effective. Although there is no legal barrier to transplantation in the undocumented based on the National Organ Transplant Act of 1984, there is an effective barrier—particularly financially for those without insurance coverage—owing to concerns about ability to afford not just the transplant, but posttransplant medications and the associated social circumstances. By contrast, there are no barriers to organ donation based on citizenship status, so the undocumented can contribute to the organ pool, but have significant limitations to benefit from it.

In 2014, Illinois became the first state to list undocumented patients for kidney transplant. The rationale behind this move was based not only on ethics, but also on economics: for Illinois, transplant is the cheaper option for each patient who receives dialysis for at least 2.7 years (7). In fact, if a patient lives at least 8 years, transplantation would save $321,000 per patient—and we expect patients to live much longer than 8 years (8).

The counterargument to listing undocumented immigrants for transplant is the perception that they would not do as well as citizens given their circumstances, access to medications, and care—and may be deported where the access to care may even be worse. However, Shen and colleagues conducted a study comparing a group of US citizens and permanent residents to the undocumented and found that undocumented immigrants actually had a greater graft survival rate when results were unadjusted. And no increased rate of graft loss was observed when the findings were adjusted for demographics, comorbid conditions, dialysis, and transplant-related factors (9).

Politics and kidney care

There are other, more politically minded arguments against having undocumented immigrants become transplant recipients. One of the arguments concerns supply and demand.

If there are over 100,000 patients on the transplant waitlist with only 12,000 patients being transplanted per year, is it fair to allow undocumented patients in the pool to increase the waitlist size? Shen and colleagues also found that undocumented patients were more likely to have a living donor (60%), and the addition of undocumented patients increased the waitlist by only 3% (9).

Additionally, if these individuals add to the donor pool by donating organs when they die, is it fair for them to not be able to receive an organ if needed? If transplantation is cost-effective and living donors are more available for this population, wouldn't this be potentially low-hanging fruit to help save and improve lives while cutting costs?

Taxpayer funding of healthcare for the undocumented is controversial, to say the least. However, it should be noted that undocumented immigrants contribute nearly $12 billion in taxes, with $2.4 billion directed toward Medicare (9). They also generate a surplus in the magnitude of billions in Social Security programs, and from 2000 to 2011, generated a $35.1 billion surplus in the Medicare Trust Fund (10).

They also have a very high rate of employment: 94% are employed, and they make up about 5% of the total civilian labor force (11). Yet, when they are subjected to emergency-only dialysis, the employment rate drops significantly from >90% to about 14% due to the burden of illness and the irregularity of their schedule given their dependence on care (5). Regardless of stances on immigration status, being sick and having access to suboptimal care would appear to result in a significantly increased financial burden than would having access to more standardized treatment options.

Our system isn't working. So what do we do to fix it? What are the next steps?

We advocate. We educate. We demand a national policy for ESRD in the undocumented population (12). We ask that we be able to treat the sick as equal, and by ethics, we should not be obligated to restrict care based on citizenship status.

Mukta Baweja is an Assistant Professor of Medicine and Nephrology at the Icahn School of Medicine at Mount Sinai in New York City. She serves on the Public Policy and Advocacy Committee of the American Society of Nephrology. She is passionate about the changing landscape of public health and improving healthcare delivery. Twitter: @muktabaweja

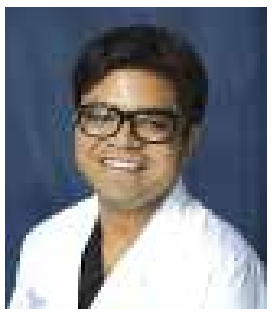
References

1. Ra R. Dialysis for undocumented immigrants in the United States. *Adv Chronic Kidney Dis* 2015; 22:60–65.
2. Hurley L. Care of undocumented individuals with ESRD: A national survey of US nephrologists. *Am J Kidney Dis* 2009; 53:940–9.
3. Gray N. Cruel carousel: The grim grind of "compassionate" dialysis. *AMA J Ethics* 2018; 20:E778–779.
4. Zuckerman S. Undocumented immigrants, left out of health reform, likely to continue to grow as share of the uninsured. *Health Affairs* 2011: 10:1997–2004.
5. Sheikh-Hamad D1. Care for immigrants with end-stage renal disease in Houston: A comparison of two practices. *Tex Med* 2007; 103:54–8.
6. Cervantes L, et al. Association of emergency-only vs standard hemodialysis with mortality and health care use among undocumented immigrants with end-stage renal disease. *JAMA Intern Med* 2018; 178:188–195.
7. Ansell D. Illinois law opens door to kidney transplants for undocumented immigrants. *Health Affairs* 2015; 34:781–787.
8. Ellena A, Linden M. Kidney transplantation in undocumented immigrants with ESRD: A policy whose time has come? *Am J Kidney Dis* 2012; 60:354–359.
9. Shen JI. Association of citizenship status with kidney transplantation in Medicaid patients. *Am J Kidney Dis* 2018; 71:182–190.
10. Leah Zallman, et al. Unauthorized immigrants prolong the life of Medicare's trust fund. *J Gen Int Med* 2015; 31:122–127.
11. Passel J, et al. Size of U.S. unauthorized immigrant workforce stable after the great recession. Pew Research Center 2016. http://www.pewhispanic.org, accessed Nov. 30, 2018.
12. Cervantes L. The United States needs a national policy on dialysis for undocumented immigrants with ESRD. *Am J Kidney Dis* 2018; 71:157–159.

Fellows Corner

Medical Graduates, the Immigration Backlog, and Nephrology

By Nikhil Agrawal and Harini Bejjanki



Nikhil Agrawal

Harini Bejjanki

The percentage of international medical graduates (IMGs) is higher in nephrology than in any other major subspecialty in internal medicine. IMGs accounted for 62% of nephrology fellows in 2017, compared with a nearly even split with American medical graduates (AMGs) in 2007.

Thirty-one percent of nephrology fellows, or half of IMGs in nephrology, are dependent on visas. This means that 1 in every 3 nephrology fellows requires an employer who can sponsor a work visa, either H1b or J1. Thus, the issues outlined here are not limited to a handful of nephrologists, and they have a major impact on the present and future of nephrology in the United States.

All the statistics listed in this article are from the American Society of Nephrology Workforce Survey, and these numbers have remained largely unchanged over the past 4 years.

For the uninitiated, H1B is a work visa, and J1 is an exchange student visa. Residency and fellowship programs may or may not support either form of visa for their trainees.

After training, fellows who require a J1 visa must work for 3 years in an underserved area before becoming eligible for permanent residency. The H1B visa does not come with such a restriction, but it has an 85,000 annual cap each fiscal year. Because the number of H1b applicants is usually higher than that, applicants go through a random lottery system.

In 2018, the United States Citizenship and Immigration Services accepted petitions for 5 working days, from April 2 to April 6, and reached the annual cap of 85,000 on April 6. This cap and lottery are not applicable if the employer is an institution of higher education or a nonprofit organization, making these employers much preferred by H1B workers. Once a physician is fortunate enough to find the right employer, an employment-based permanent residency, or green card, can be applied for.

The number of green cards available each year is limited. The majority are reserved for family-based categories, whereas a small fraction are available for the highly diverse group of employees trying to get permanent residency in the United States. There is a 7% per country limit, which means that no more than 7% of the visas for green cards may be issued to natives of any one country in a fiscal year, regardless of individual merit. As one can imagine, this puts immigrant physicians from large countries into an ever-increasing backlog for green cards.

This backlog is particularly large for citizens of India. India also happens to be the largest source of IMGs in nephrology; 81 of the 267 nephrology IMGs in the 2017 ASN workforce survey attended medical school in India. Currently, the wait time for an Indian physician to get a green card is anywhere from 20 to 150 years! In brief, these physicians will be visa-dependent for decades, and the issues outlined here are not temporary.

This green card backlog and chronic visa dependency have profound effects on nephrology, nephrologists, and their employers.

Impact on fellowships

It starts with fellowship applications. Because nephrology fellowships are relatively noncompetitive, more fellowship programs are willing to accept candidates requiring visas. This means that IMGs requiring visas have a higher chance of getting into reputable universities as nephrology fellows. This helps nephrology programs attract more visa-dependent applicants—but without permanent residency or citizenship, fellows do not have access to additional years of research on T32 grants. A T-32 enables institutions to make National Research Service Awards to individuals (U.S. citizens or permanent residents) selected by them for predoctoral and postdoctoral research training in specified shortage areas. Decades-long visa dependency also leads to ineligibility for National Institutes of Health grants during and well after graduation, making basic research even less attractive for IMG fellows and discouraging an ever-shrinking pool of trainees who are interested in pursuing nephrology research as a career path. This is surely a major reason why AMGs are significantly more likely than IMGs to report that they plan to continue their current fellowships (22.7% vs. 11.8%).

Clinical nephrology also presents several challenges for the IMG. An IMG with either an H1B or a J1 visa finds that the number of suitable job positions is limited. Employers are often not in desired locations, and 55.4% of IMGs reported having difficulty finding positions they were satisfied with, compared with 28.8% of AMGs. "Lack of jobs/practice opportunities that meet visa status requirements" was one of the top reasons. Forty-four percent of IMGs reported changing their plans because of limited nephrology job opportunities. In contrast, there are abundant jobs around the country in hospital medicine, and eligible IMGs are attracted to hospital medicine because of the ease of finding a job in a desired location, the higher pay, and flexible schedules. Therefore, we are seeing a trend whereby IMG nephrologists are choosing to work as hospitalists. For employers, this backlog brings a perennial source of expense, paperwork, and the uncertainty of sponsoring a visa.

There is also a growing emphasis on innovation in nephrology. What if a visa-dependent nephrologist comes up with an innovative idea for a product, service, or business venture? Under the immigration laws, nephrologists with H1B visas are permitted to work only for their sponsoring employers, which means that working toward realizing an innovative idea becomes unpaid voluntary service.

These are some of the ways the green card backlog is adversely affecting the present and future of nephrology in the United States. Multiple potential legislative solutions have been around for many years. We can hope that legislation to clear these backlogs will provide a much-needed boost to our beloved specialty. But until then, we keep calm and carry on.

Nikhil Agrawal is transplant nephrology fellow at Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, Massachusetts. Harini Bejjanki is a clinical nephrology fellow at the University of Florida, Gainesville, Florida.

Suggested Reading

1. https://www.asn-online.org/education/training/workforce/Nephrology_Workforce_Study_Report_2016.pdf
2. https://www.asn-online.org/education/training/workforce/Nephrology_Workforce_Study_Report_2015_Summary.pdf
3. https://www.asn-online.org/education/training/workforce/Nephrology_Fellow_Survey_Report_2017.pdf

Findings

How to Handle the Creatinine "Bump"—Analysis of ACCORD-BP Data

For patients with type 2 diabetes, increases in serum creatinine after starting blood pressure–lowering treatment—even greater than 30%—do not necessarily mean that antihypertensive therapy should be decreased, reports a study in *Hypertension*.

The researchers performed a post hoc analysis of data from the ACCORD-BP (Action to Control Cardiovascular Risk in Diabetes Blood Pressure) trial, which compared intensive versus standard BP-lowering therapy (systolic BP cutoffs of 120 and 140 mm Hg, respectively). The analysis included 4733 patients with type 2 diabetes. Mean age was 62.2 years, with a mean estimated glomerular filtration rate of 81.5 mL/min/1.73 m^2.

Patients were classified into three groups, based on the extent of increase in serum creatinine from baseline to 4 months: less than 10%, 10% to 30%, and more than 30%. The effects of creatinine increase during antihypertensive therapy on a primary outcome of all-cause mortality, major cardiovascular events, and renal failure were analyzed. Mean follow-up was 4.9 years.

Follow-up data were available for 4446 patients: 2231 assigned to intensive BP control and 2215 to standard treatment. Neither group showed an association between serum creatinine increase and the risk of adverse outcomes.

Patients with a serum creatinine increase greater than 30% had a higher rate of adverse outcomes, with no difference between the intensive and standard therapy groups: hazard ratios were 1.32 and 1.47, respectively. There was no significant association for patients with a 10% to 30% increase.

Previous studies have linked an initial serum creatinine increase during antihypertensive therapy to an increased risk of adverse outcomes. These reports led to recommendations to reduce antihypertensive therapy for patients with serum creatinine increases of greater than 30%.

The new analysis finds that serum creatinine increase of greater than 30% is associated with higher risks, with similar increases for patients receiving intensive versus standard antihypertensive therapy. "These data suggest that a serum creatinine increase that coincides with a lower BP should not be interpreted as harmful and lead to a reduction in BP-lowering medication," the researchers write. They call for further studies to assess the optimal cutoff point for serum creatinine increase after antihypertensive therapy.

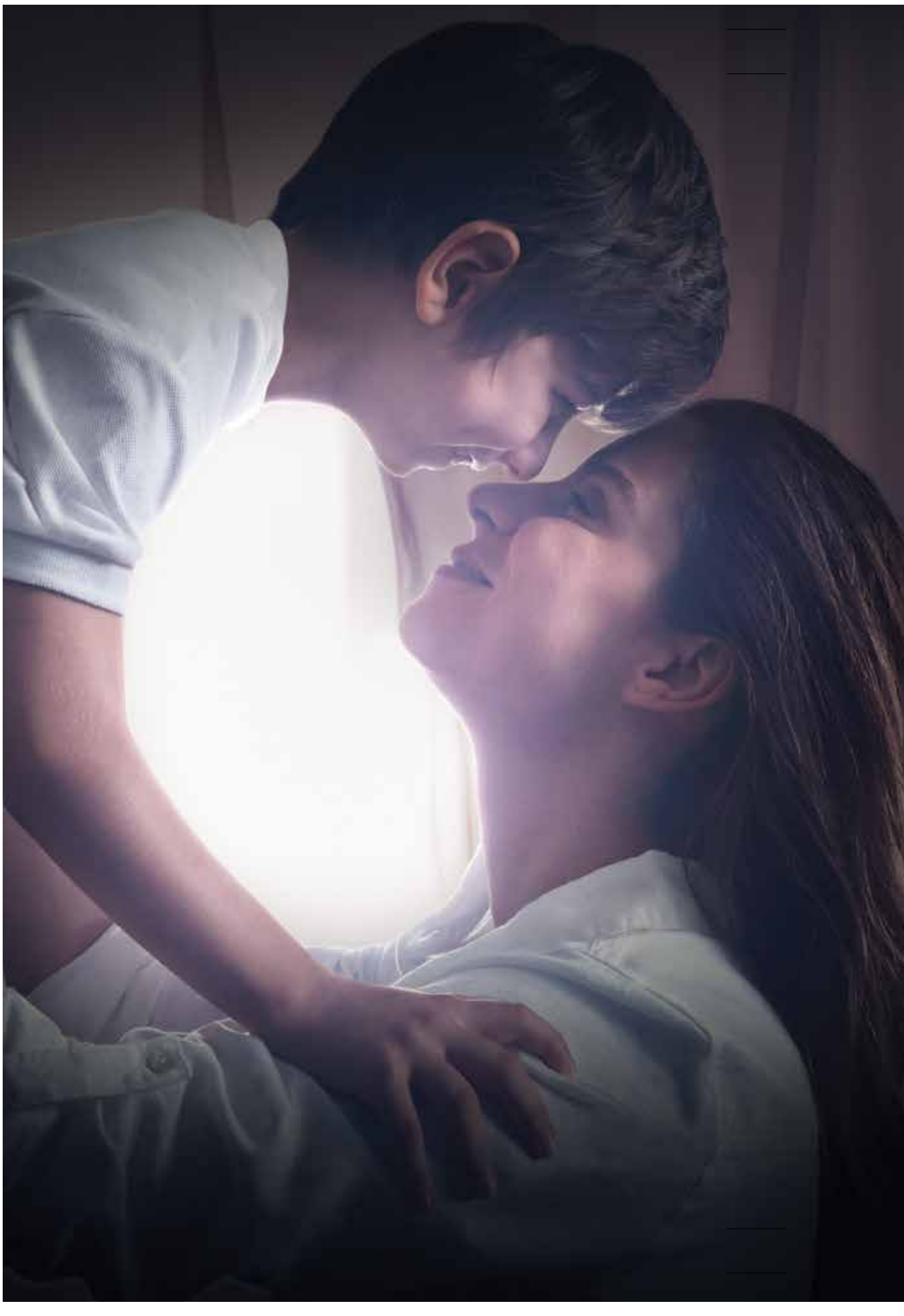
In an accompanying editorial [*Hypertension* 2018; 72:1274–1276], Drs. George L. Bakris and Rajiv Agarwal discuss the implications for managing the creatinine "bump" after antihypertensive therapy. They conclude: "What we learn from the ACCORD analysis is that a rise in serum creatinine of >30% is a marker of future nonrenal morbidity and mortality. What we do about it is a matter of clinical judgment" [Collard D, et al. Creatinine rise during blood pressure therapy and the risk of adverse clinical outcomes in patients with type 2 diabetes mellitus: a post hoc analysis of the ACCORD-BP randomized controlled trial. *Hypertension* 2018; 72:1337–1344].

Exome Sequencing Reports High Rates of Kidney/Urinary Tract Variants

Nearly one-fourth of healthy adults participating in exome sequencing studies have "purportedly pathologic" variants associated with kidney and genitourinary diseases, according to a report in *Annals of Internal Medicine*.

The investigators performed a secondary analysis of exome sequencing data in 7974 adults who identified themselves as being in good health. Participants were enrolled mainly as healthy controls for genetic studies or as healthy family members of probands with suspected genetic diseases not involving the kidney or genitourinary tract. Exome data were analyzed for the presence of candidate pathologic variants of 625 genes linked to kidney and genitourinary disorders. The variants were identified from the Online Mendelian Inheritance in Man (OMIM) and Orphanet databases.

A potentially pathologic variant was reported for 23.3% of this sample of healthy adults. These consisted mainly of variants with "implausibly high allele frequencies." The 25 most commonly reported genes—all discovered before release of the Exome Aggregation Consortium database—accounted for about two-thirds of participants with candidate variants.



Even after application of a more "stringent filtering pipeline," 112 candidate variants were reported for 1.4% of participants. On manual classification, 63% of these variants were classified as being of unknown significance, 26% as pathogenic or likely pathogenic, and 11% as benign or likely benign. Manual classification identified variants that could lead to clinical follow-up in 176 participants. Clinical data were available for 26 participants; only 1 had confirmation of a genetic diagnosis (neurofibromatosis) without further clinical review.

Exome or genome sequencing can lead to incidental findings unrelated to the primary indication for sequencing. This study finds candidate variants previously reported as associated with kidney and genitourinary diseases in 23% of a large sample of self-reported healthy adults.

"Widespread reporting of incidental genetic findings related to kidney and genitourinary disorders will require stringent curation of clinical variant databases and detailed case-level review to avoid genetic misdiagnosis and unnecessary referrals," the investigators conclude. They call for similar studies of gene variants relevant to other medical subspecialties [Rasouly HM, et al. The burden of candidate pathogenic variants for kidney and genitourinary disorders emerging from exome sequencing. *Ann Intern Med* 2018; doi: 10.7326/M18-1241].

Industry News

AstraZeneca's kidney blitz

AstraZeneca (Cambridge, UK) is emphasizing its dedication to chronic kidney disease (CKD) and related conditions. In a sign of its focus on the "R" in its renamed division, Cardiovascular, Renal, and Metabolism (CVRM), the company offered research and information in 35 separate scientific articles and data presentations during Kidney Week 2018.

Formerly known as CVMD (cardiovascular, renal, and metabolic diseases), the division was renamed in early 2018. Renal work has become an urgent area of concern, said Elisabeth Bjork, vice president of CVRM for Global Medicines Development. "Deaths due to CKD specifically more than doubled between 1990 and 2013," she said. "Renal patients are at risk for life-threatening complications, with even small decreases in renal function leading to an increased risk of death and CV-related complications once moderate renal dysfunction has been reached (eGFR <60 mL per minute per 1.73 m^2)."

The data presented at ASN Kidney Week "demonstrate our ambition to advance treatment for patients with chronic kidney disease and its associated complications," said Danilo Verge, vice president of CVRM for Global Medical Affairs. "We are exploring solutions to help address unmet medical needs, including disease modification during early-stage diagnosis to managing potentially life-threatening complications as patients progress to dialysis and end-stage renal disease."

These are among the company's areas of interest:

- Lokelma (sodium zirconium cyclosilicate) for hyperkalemia,
- Anemia in CKD,
- Farxiga (dapagliflozin) effects, and
- Early science (collaboration with Ionis Pharmaceuticals) on antisense oligonucleotides as a potential modality for new targets in CKD and identifying kidney cell subpopulations.

AstraZeneca states its goal as understanding "more clearly the underlying links between the heart, kidneys and pancreas….Our ambition is to modify or halt the natural course of CVRM diseases and potentially regenerate organs and restore function."

Zacks Analyst business blog recently noted that "AstraZeneca's shares have gained +8% in the year to date, outperforming the Zacks Large Cap Pharmaceuticals industry which has gained +3.2% over the same period." The site highlighted that several launches are under way across CVRM, oncology, and respiratory. The company's diabetes franchise faces "stiff competition," which in part may explain its foray into other areas.

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

Winning the ASN Policy Races for 2018

1. **Enacted law for telehealth reimbursement**
   Allowed you to be reimbursed for seeing home dialysis patients via telehealth starting January 2019

2. **Opposed proposals to devalue cognitive care reimbursement**
   Fought to protect you from Medicare proposal to drastically lower E&M payments

3. **Increased funding for kidney research**
   Grew your pool of research funding, securing a $3B increase for the NIH, with a substantial increase for NIDDK

4. **Launched KidneyX to foster innovation**
   Partnered with the federal government to accelerate the development of new kidney therapies to improve the lives of your patients through a series of prize competitions

5. **Protected your latitude to prescribe home dialysis**
   Fought ill-informed Medicare contractors' Local Coverage Decision proposals limiting access to home dialysis

6. **Improved veterans' access to transplantation**
   Secured passage of law veterans and their living organ donors to receive transplant services at closer-to-home transplant centers

7. **Advanced protections for living organ donors**
   Secured Congressional report language clarifying that living donors should qualify for Family Medical Leave Act protections

8. **Created new tools to improve patient empowerment**
   Partnered with the Department of Veterans Affairs Center for Innovation to develop a new mobile app to empower your patients by tracking nutrition, fitness and medication information

9. **United Kidney Community on Capitol Hill**
   Brought together ~20 patient and health professional organizations for fourth annual Kidney Community Advocacy Day to advocate for you and your patients

10. **Informed you of ASN's advocacy on your behalf**
    Launched the monthly Policy and Advocacy Insider email newsletter to keep you abreast of what ASN is doing for you and how you can get involved

Legislative Action Center, Podcasts, and Updates

Stay up to date on policy developments affecting you and your patients.
It's easy on the ASN Advocacy site, ***www.asn-online.org/policy***.

ASN

Classified

Nephrologist for Growing Practice

Growing nephrology practice in Mississippi looking for a physician. Great benefit package. Please email for more information, wlong@nephrologyms.com.

ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

CLASSIFIED ADVERTISING WORKS!

contact Rhonda Truitt
rhonda.truitt@wt-group.com
443-512-8899 x. 106

KidneyNews Classified Advertising Information

Classified space is for advertising positions available, open faculty positions, course announcements, seminars, meetings and educational courses.

Display Advertising Rates

Ad Size	1x	3x
Full Page	**$2,675**	**$2,485**
1/2 Page	$1,765	$1,575
1/3 Page	**$1,525**	**$1,455**
1/4 Page	$1,275	$1,155
1/6 Page	**$1,095**	**$1,085**

Line Advertising Rates

Contact for Rates

Closing Date & Cancellations:
Copy must be received six weeks in advance of the month in which the ad is to appear. Cancellation requests must be made in written form by fax, e-mail or postal mail and will be honored for the earliest applicable issue.

All Ads Must be Prepaid

Contact:
Rhonda Truitt
rhonda.truitt@wt-group.com
P: 443-512-8899 x. 106 F: 443-490-4003

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 **Return the completed form to:**
Bob Henkel, 1510 H Street NW, #800, Washington, DC 20005
or Fax: 202-403-3615 or Email: bhenkel@asn-online.org

Index to Advertisers

Preventing infections is essential for patient safety.

How many days since your last infection?

NTDS and CDC's Making Dialysis Safer for Patients Coalition have created a new resource in the fight to eliminate bloodstream infections.

The "Days Since Infection" Poster offers one way to raise awareness about bloodstream infections in your dialysis facility with both your staff and patients.

It provides immediate feedback to front line staff to do all that is possible to target zero preventable infections.

The poster can also be used to start discussions and provide education about the importance of preventing BSIs with patients and family members.

The poster is available in two sizes and you have the option to add your organization's logo. Laminated copies of the print version can also be ordered for free at **www.cdc.gov/dialysis/clinician/index.html**

Share a photo of the poster at your facility on social media using #ASN_NTDS, #DialysisPatientsFirst, #targetzeroinfections.

NTDS
NEPHROLOGISTS TRANSFORMING DIALYSIS SAFETY