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Medical Students Lead Effort to Remove Race from Kidney Function Estimates

By Bridget M. Kuehn

When a lecturer at the University of Washington School of Medicine described the use of black race as an adjustment in estimated glomerular filtration rate (eGFR) calculations, it made medical student Naomi Nkinsi uncomfortable. The use of race as a proxy for muscle mass hearkened back to racist comments she'd heard suggesting that black people have more muscle or are otherwise biologically different.

"I was thinking how is this something we are using to measure someone's kidney function, something that we are using to determine if they can get medication, if they can get transplant or treatment?" said Nkinsi, who is also working on her masters degree in public health at the school. "In medicine we talk about precision. When it comes to race, people throw that out the door. Being black, or race, is used as a proxy for so many other things."

Nkinsi is not alone in feeling the use of race, a social construct rather than a biological one, in estimating kidney function is inappropriate. Many other current and former black medical students at her school and others have questioned this practice. In fact, a growing movement led by US medical students across the country is working to eliminate the use of race as an adjustment in eGFR. As of June 2020, the University of Washington, Massachusetts General Hospital, and Brigham and Women's Hospital became the latest institutions to abandon the use of race in kidney function estimations. Previously, the Beth Israel Deaconess Medical Center in Boston and Zuckerberg San Francisco General Hospital (1) made similar changes.

"This is a momentous change where UW Medicine is leading the way," said Rajnish Mehrotra, MD, interim head of the division of nephrology at the University of Washington School of Medicine in a statement (2).

Calls for change

There has been growing skepticism of the use of black race in kidney function estimation among nephrologists. In a viewpoint published in *JAMA* in June 2019, Nwamaka Eneanya, MD, MPH, and colleagues argue that using race as a variable may restrict access to care for some patients and interfere with transparency in patient care (3). Eneanya is assistant professor of medicine and epidemiology at the University of

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The Inside Story: ***How New York Nephrologists, National Suppliers Made Creative Adaptations to Cope with COVID-19 Surge***

By Eric Seaborg

As COVID-19 patients began to flood New York City area hospitals in February, they developed acute kidney injury (AKI) at rates much higher than anyone expected from a respiratory virus. By mid-April, the need for renal replacement therapy in these patients was pushing the system to the breaking point, as healthcare providers and manufacturers scrambled to find equipment and supplies.

Hospitals used creative means to cope—including contacting the top decision-makers at the largest companies directly to plead for help and finding ways to treat more patients with a limited number of machines.

Because COVID-19 is categorized as a respiratory infection, a great deal of attention was given to the need for ventilators early on. Reports from China and Italy did not indicate that AKI was a major concern, so American nephrologists were taken by surprise at the high rate of AKI when COVID-19 patients poured in.

A link to *Kidney International* of COVID-19 patients

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Medical Students

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Pennsylvania's Perelman School of Medicine in Philadelphia. Another perspective in the *Clinical Journal of the American Society of Nephrology* by Vanessa Grubbs, MD, MPH, links this practice to the troubling history of racism in medicine (4). Grubbs is associate professor in the division of nephrology at the University of California, San Francisco.

"It all traces back to this legacy of trying to put biology into race," Grubbs said. "Instead, race is a social construct that has been used to justify atrocities against certain groups of people. It is an insidious thing that has been going on since the beginning of the country."

Eneanya and her coauthors state in their viewpoint that equations that use race to estimate kidney function such as the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) and the older Modification of Diet in Renal Disease Study (MDRD) equation were created using large cohorts of patients who underwent measurements of their true glomerular filtration rate. Black race was associated with slightly higher GFR even when patients had the same blood creatinine levels, which was attributed to higher average muscle mass. As a result, the CKD-EPI with race adjustment increased the eGFR of black patients by about 16%.

There is evidence that using race increases the statistical accuracy of kidney function estimates (5), according to Peter Reese, MD, associate professor of medicine at the Perelman School of Medicine and co-author of the *JAMA* viewpoint. However, the decision to use the idea of black race as a proxy for muscle mass was never openly debated and raises ethical concerns about perpetuating the concept that race is a biological rather than a social construct.

"To build it right into an equation that gets used many millions of times a day just reinforces the bogus concept," Reese said.

Additionally, the way race is assigned in medicine is often problematic. For example, a clinician may assign race based on a patient's skin tone or hair or by the way the patient chooses to identify, notes Eneanya. But this does not take into account ancestry.

"It just lumps all black people together in a way that it doesn't matter if you have two black parents, or you're biracial, or just your great grandparent was biracial and everybody else was white," Grubbs said.

In fact, nephrologist Malika Mendu, MD, assistant medical director for quality and safety at Brigham and Women's Hospital, noted that the use of race adjustments in eGFR were based on studies in a few hundred patients who were classified as black by researchers, which raises questions about how representative these patients are of individuals who self-identify as black. When Mendu and a colleague analyzed the potential impact of the use of race in eGFR on patients in the hospital system, it raised concerns that fewer black patients were being referred for transplant care as a result of the adjustment.

Eneanya, Reese, and Grubbs share concerns that use of race may contribute to delayed referrals to kidney care or transplant for some black patients.

In her book *Hundreds of Interlaced Fingers* (6), Grubbs writes about a very muscular black male patient who over the course of his kidney disease experienced muscle wasting. She chose to use a non–race-adjusted eGFR and referred him for transplant evaluation, something that would have been delayed by 2 years based on his race-adjusted kidney function.

For patients with higher kidney function, the race-based adjustment is less likely to change their care, Eneanya noted. But when using the race-based adjustment would change their care, it is important for physicians to be transparent.

"I'm quite transparent with my patients about many things, not just race and eGFR, especially if they're lying right on the border [of being referred for transplant or dialysis planning] and their race is making a difference," she said. "I've talked to my patients about that and I usually do some confirmatory testing, either cystatin C or urinary creatinine clearance, to confirm where their kidney function is."

Pursuing alternatives

The change at the University of Washington School of Medicine was the result of many years of advocacy by black students to address racism in the curriculum and in medicine, including a 2016 sit-in, noted Nkinsi. The protest gave rise to creation of the school's Anti-Racism Action Committee (7), which is made up of medical students, faculty, and staff who work together to identify and eliminate racism.

"It's our responsibility as students and faculty in academic medicine to take a second look at all of our curricula and make sure that we're not using race in inappropriate and unconstructive ways," said Elizabeth Stein, a medical student who co-chaired the committee.

The committee worked with faculty in family medicine, laboratory medicine, pathology, and nephrology to assess the use of race in eGFR and together determined that "use of race in the biomedical environment is an imprecise variable and does not meet the scientific rigor UW Medicine expects of diagnostic tools," according to a statement (2). As a result, its laboratories have shifted from use of the MDRD equation to the CKD-EPI equation without race as a variable.

Stein acknowledged that the new equation is "still not perfect" and that more research on better alternatives is needed. "The move by University of Washington Medicine signals that we can move beyond race-based medicine and actually practice something closer to evidence-based medicine," she said.

Public efforts by hospitals to eliminate race-based medicine are an important way to begin to rebuild trust with black communities.

In 2017, medical students at Beth Israel Deaconess Medical Center in Boston lobbied for a similar change after students in its Racial Justice Coalition raised questions about the use of race in kidney function estimations, according to Leo Eisenstein, MD, who was a medical student and member of the coalition.

"[There] was a clear conflict in the curriculum in how race was described as a very unreliable proxy for genetics and the way race is used every day in medicine as a proxy for genetics," said Eisenstein, who is now a resident at New York University Bellevue Hospital. Nephrologist Melanie Hoenig, MD, associate professor of medicine, helped champion the students' efforts and helped them work with faculty and multiple departments at the medical center. Eistenstein and his fellow coalition members also worked with faculty and multiple departments at the medical center. As a result, the center chose to report eGFR as a range between the race-adjusted and unadjusted values. This allows clinicians to take into account factors like an individual patient's muscle mass or nutritional status in determining where patients likely fall on the range, he said. Physicians also receive a note explaining that patients with greater muscle mass or better nutritional status are likely to be near the higher end of the range.

"It takes away the need for this dubious assessment of each patient's race," Eisenstein said. "It restores attention to the relevant physiological differences such as muscle mass that are thought to bear on differences in serum creatinine."

Eneanya said she hopes many more institutions will follow in the footsteps of the University of Washington and other schools that have made such changes. "I'm glad that this momentum is now turning into action," she said. The decision to eliminate the use of the race multiplier at Mass General and Brigham and Women's Hospital piggybacked off that work and was also a team effort involving multiple individuals and departments, said Michelle Morse, MD, MPH, assistant professor at Harvard Medical School. She presented a Grand Rounds on research that critically assessed the studies used to support the notion of higher muscle mass in black patients by Cameron Nutt, MD, who is was one of the medical students working on the effort at Beth Israel and is now a fellow at Brigham. Brigham's Health Equity committee, which Morse co-chaired, funded Mendu's research, which led to the decision to remove a notation about race adjustment in their medical record system and instead use the unadjusted number.

Grubbs also commended the move: "I'm really thrilled to see that the medical students were able to get the support they needed to make effective change."

Grubbs recommended that hospitals eventually switch to using cystatin C, which she and her colleagues use at Zuckerberg San Francisco General, to calculate kidney function. She noted it provides a cleaner result than using creatinine. Eneanya agreed cystatin C is one alternative that should be considered, although she noted it is not widely available yet at many hospitals. Grubbs acknowledged that cystatin C can have a longer turnaround time than creatinine and is more expensive, costing about 25 cents per test compared to 5 cents for creatinine. Mendu has also recommended a shift to using cystatin C at Brigham.

"My hope is that if there is more demand for it, then people will be more familiar with it and be able to run tests faster onsite," Grubbs said. She noted that several other academic medical centers across the country are considering removing the use of race in eGFR calculations.

Ultimately, many are hopeful these changes will improve patient care. "We expect earlier referral for black patients and better chronic kidney disease care and transplant outcomes," said Morse.

Public efforts by hospitals to eliminate race-based medicine are an important way to begin to rebuild trust with black communities, who may lack confidence in clinicians because of historical breaches of trust, Nkinsi noted.

"The fact that programs are actively trying to rectify these issues is something that will help build that trust in the communities, and hopefully help repair those bridges that have been burned," Nkinsi said. But, she noted, that is just the starting point; more community outreach is needed. She also said it is important to acknowledge that too often the voices of black students, faculty, and community members have been ignored or discounted.

Eneanya said physician advocacy is essential to these efforts.

"We have to take a stand on issues that have been overlooked and ignored previously to this point," she said. "We're moving beyond the path of just describing health inequities and it's time to take action, whether it be developing equations that don't use race or being more transparent with your patients when discussing these issues. It's time for us to take a stand." ■

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COVID-19 Surge

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admitted to the 23 hospitals in New York's Northwell Health system reported that of 5449 patients admitted, 36.6% developed AKI, and 5.2% of the total—some 285 patients—required dialytic support.

A study in *CJASN* that included several hospital systems reported: "An informal survey of our intensive care units (ICUs) this week demonstrates that 20%–40% of intubated ICU patients have AKI that necessitates kidney replacement therapy."

Steven N. Fishbane, MD, chief of the division of nephrology at Northwell Health, said he tried to plan ahead and order equipment for 10 of the hospitals in the system: "About two weeks before the wave really hit us, we modeled out what it would look like if this hit us a soft glancing blow, if it hit us medium, or if it hit us with complete fierce intensity. I remember looking at it and thinking, oh God, in the worst model, we would need about 60 new portable dialysis machines, 60 new portable reverse osmosis machines, [and] 24 new CRRT machines. I spoke to our procurement people and they said to order the entire thing." The machines arrived in time to be put into use before the biggest wave of patients arrived—and that wave proved to be about 10% worse than even his worst-case scenario, Fishbane said.

Finding ways to stretch resources

As the patient census grew so much that they were running out of continuous renal replacement therapy (CRRT) machine capacity, Fishbane emailed CRRT experts around the country for suggestions on how best to use his resources. One expert suggested adapting hemodialysis machines to provide CRRT in the ICU through sustained low-efficiency dialysis (SLED)—providing dialysis over eight hours instead of the normal three- or four-hour session. "You make it gentle enough and slow enough, so that very sick patients can tolerate it," Fishbane said. Having the machine in the ICU with several patients receiving treatment helps ease the nurse-to-patient ratio, Fishbane said, "because each of the ICU nurses has responsibility over the patient and a little bit of responsibility overseeing the dialysis. Then you have one hemodialysis nurse who walks around the unit and oversees the whole operation." If the ICU nurse encounters an alarm, they can find the hemodialysis nurse for help.

Another adjustment that saved staffing was cohorting, Fishbane said. When the dialysis unit could not accommodate the overflow of patients, dialysis patients were grouped together in a room where one dialysis nurse could provide their care needs. Staffing was a constant problem with not only the increased number of patients, but staff becoming unavailable when they were out with their own COVID-19 infections.

Jai Radhakrishnan, MD, clinical director of nephrology at Columbia University Irving Medical Center, said that his institution also ordered some 40 NxStage machines for CRRT as well as hemodialysis machines for the various hospitals in his system. But even those new machines could not keep up with demand.

Many patients received prolonged intermittent RRT rather than CRRT. "You would give patients either a 12- or 24-hour and then flip the machine to the next patient," so one machine could serve two patients, Radhakrishnan said.

Radhakrishnan's team also used SLED with hemodialysis machines, a move that enabled them to remove three or four patients a day from the CRRT census. For patients well enough to receive hemodialysis, their treatment frequency was reduced from three times a week to two.

Fishbane and Radhakrishnan both avoided using peritoneal dialysis because of staff unfamiliarity with the procedure and potential incompatibility with the need for a prone position for patients on ventilators, but some institutions found it helpful.

"Peritoneal dialysis has a long history as a successful modality for the treatment of acute kidney injury, but it has gone out of favor over the last 20 years," said David S. Goldfarb, MD, clinical chief of nephrology at New York University Langone Health and chief of nephrology and director of hemodialysis at the New York Harbor Veterans Administration Medical Center. "We were able to put together teams of people who were not dialysis technicians or dialysis nurses, people deployed from other services, who learned how to do manual exchanges of PD. The advantage of PD is that it is relatively low tech [and] is easy to teach people how to do it." The *CJASN* paper reported that 22 patients were on PD at Bellevue Hospital Center, six at the New York campus of the New York VA Healthcare system, and four at the NYU Langone-Manhattan campus.

A critical need for fluids

Goldfarb said the use of PD helped remove pressures on their hemodialysis staff and CRRT supplies. As the surge in patients continued, the need for—and difficulty finding—dialysis supplies was a growing challenge.

Radhakrishnan said that although his institution ordered more machines, it did not occur to them to stock up on fluids. When manufacturers found it difficult to meet the unexpected needs, his institution did what it could to reduce fluid use. They reduced prescriptions in CRRT from the standard flow of 20 to 25 milliliters per kilogram per hour to 15. The use of prolonged intermittent renal replacement therapy (PIRRT) and the reduction in hemodialysis frequency also saved supplies.

Radhakrishnan said that an "Excel genius" in his division calculated the optimum number of bags to use at a certain fluid rate per hour to utilize the bags most efficiently. "This spreadsheet would tell you that for this fluid prescription, hang so many bags, and don't exceed that, so that led to a drop in the consumption from wastage," he said.

They even found a significant way to save both fluid and cartridges by working with hematologists to change a blood test. COVID-19 is associated with a remarkable amount of blood clotting, despite heparin treatment. Radhakrishnan's hospital switched from monitoring heparin efficacy using the standard activated partial thromboplastin time to using an anti-factor Xa test, which Radhakrishnan called a more specific target of heparin efficacy. He said the new tests revealed that many patients needed "a heck of a lot more heparin. We circulated this protocol across the campuses and there was an immediate drop in the number of wasted cartridges."

Columbia Medical Center also went outside its usual supply chain and ordered home dialysis fluid from B. Braun and adapted it for use. They held weekly meetings with their suppliers, but there was only so much the suppliers could do when New York City hospitals were using five times as much dialysis solutions as usual.

Easter crisis

As supplies dwindled and patients continued to fill the wards, on April 11, 2020, the day before Easter, Radhakrishnan tweeted a call for help that began: "Dire straits in NYC!!. Shortage of dialysis nurses, CRRT machines and fluids across all hospitals."

That tweet received a lot of media attention, but there was a flurry of activity that Easter weekend happening behind the scenes. ASN had formed a COVID-19 Response Team several weeks before to work with the Centers for Disease Control and Prevention and dispense information and expert advice. The team's co-chair, Alan S. Kliger, MD, clinical professor of medicine at Yale School of Medicine said: "Several hospitals in New York came to the realization that, with the explosion they were experiencing in the need for renal replacement therapy, in the coming week or two they wouldn't have enough to treat all of the patients unless something could be done to increase their supplies. They had spoken with their suppliers, [who] had said, 'We can give you some increase in supplies, but we have to continue supplying other places in the country for their needs.'"

Baxter customers were running up against a March 25 "protective allocation" directive limiting the increase in supplies their customers could order to about 110% of their normal use. The policy was designed to prevent hoarding and ensure delivery of at least some product to all customers, but it caused consternation among New York facilities that needed several times their usual consumption.

The ASN team shared their contacts and strategized about how to respond. "What we at the ASN did was to contact directly the chief medical officers and the chief operating officers of the companies that supply those fluids to the hospitals," Kliger said. "So this is a step way above the local suppliers that the hospitals had spoken to, and their response was fabulous. Their response was, 'Of course we have to figure out how to get fluids and supplies to them, and let's work together to do that.' But they also shared with us the dilemma that they couldn't simply turn on a spigot and dramatically increase manufacture of the supplies, which meant that any substantial increase to the New York area would mean diverting supplies that were destined and contracted to go to other hospitals and cities around the country."

"The companies were remarkably collaborative," Kliger said, and within 24 hours more supplies began arriving at the hospitals experiencing the most critical shortages. At the manufacturers' request, the ASN team began surveying the hospitals "to figure out and model what over the next few weeks the needs would be. Arms of the government were also really interested in what we were doing," Kliger said.

Federal response

It took some time for the urgency and severity of the kidney treatment needs—when everyone went into the fight against this respiratory virus thinking only about ventilators—to become clear to federal agencies, said Kristen Finne, who works in the office of emergency management and medical operations in the Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response (ASPR).

But after the Easter weekend calls, one concrete contribution the federal government made was to expedite shipping from Europe, where much of the manufacture of dialysis fluid takes place. "If the fluid that was so critically needed were to go through its normal process of traveling, it would take weeks to get to a port and get on a ship, which would take about three weeks, and then have to be trucked again to its final destination," Finne said. "We said [to manufacturers], whatever you can offer as you are trying to increase your production, we will help expedite and fly it to the U.S." using flight contracts associated with the strategic national stockpile. These flights brought in about 300,000 liters of dialysis fluid.

Largely in response to the devastation of hurricanes Irma and Maria, the federal government had leased 50 of Outset Medical's Tablo devices for the strategic national stockpile. These devices were selected for the stockpile in large part for their versatile ability to deliver both conventional hemodialysis and CRRT coupled with an ability to handle both water purification and dialysate production. The stockpiled devices were deployed to New York hospitals in early May.

Many hospitals purchased the relatively new Tablo in preparation for COVID-19 thanks to its versatility and ease of use, said Chad Hoskins, general manager of home and vice president of strategy at Outset Medical: "We saw a number of situations where hospitals were taking staff who were not dialysis-trained. In one facility, an OR team was sitting idle because all elective procedures had been cancelled. They trained those nurses on Tablo to deliver dialysis, and that freed up their dialysis nurses to [concentrate on] the more critically ill patients."

The VA's Goldfarb said his facility brought in several Tablos, and he was the first staff member to operate it "because I didn't have dialysis staff to do it that day." He joked that it is so easy, "even a doctor can do it," but noted that they trained two primary care nurses who had never done dialysis to use the Tablo.

Largest suppliers adjust

The two largest manufacturers of dialysis equipment and supplies made some major adjustments in their operations in the weeks after Easter weekend.

In mid-April, Fresenius formed its own National Intensive Renal Care Reserve consisting of "approximately 150

pieces of equipment ready for rapid deployment to hospitals," said Joe Turk, president of home and critical care therapies. The equipment included a pool of NxStage critical care units, which can be used for CRRT and PIRRT, as well as NxStage System One Cyclers, which are typically used in homes or skilled nursing units, but which can provide additional capacity in ICUs.

The Food and Drug Administration provided an emergency use authorization allowing the importation and use of supplies and machines approved in Europe, and on May 11 Fresenius announced it was preparing its first shipment of the European-approved multiBic dialysate solution for CRRT.

As many critically needed supplies went to New York, hospitals in other parts of the country experienced unexpected changes in their orders, according to Anitha Vijayan, MD, a member of the ASN COVID-19 Response Team and director of acute dialysis services at Barnes-Jewish Hospital in St. Louis: "Because NxStage was experiencing shortages in bicarbonate solutions, they had to send lactate solutions to certain high-volume institutions like mine. The diversion of resources to New York meant that other institutions across the country, including mine, had to make changes in how we do continuous renal replacement therapy. Lactate solutions are not ideal to be used as a CRRT solution because lactate may be associated with more hemodynamic instability for patients who are already critically ill."

Vijayan's hospital had to draw up a policy to select which patients could be safely treated with lactate instead of bicarbonate solutions, but the change never compromised patient care, she said. That hospital was not hit as hard as those in New York, but at one point they had three COVID ICUs, and had to cross-train nurses to help with the care.

For its part, Baxter said in a statement that it has "delivered significantly more product to our hospital customers" by ramping up production of CRRT products to maximum levels. "The company has added multiple work shifts, with all facilities manufacturing products used in COVID-19 patient care running 24 hours a day, seven days a week. Baxter has partnered with its logistics providers to fly critically needed medical devices and medicines back and forth between the U.S. and Europe," a spokesperson said.

Staffing in an infectious setting

Another big challenge for the New York hospitals was simply maintaining staff levels—the huge patient census called for all hands on deck, but many key staff members contracted the highly infectious disease. Fishbane's division had seven nurses out at one point, and hospitals welcomed volunteers from other parts of the country as key contributors.

Goldfarb benefited from the VA's internal volunteer program that led to a nephrologist from New Hampshire coming to lend a hand for three weeks. The addition was especially needed because one of Goldfarb's colleagues was

down with a COVID-19 infection.

Fresenius also sent volunteers, which were particularly valuable because of their familiarity with dialysis. The chief physician at New York Presbyterian, Columbia University Medical Center publicly thanked Fresenius for providing 12 trained nurses and technicians.

The hospitals also shared capacity, Goldfarb said: "The New York VA and the Brooklyn VA were back-ups for peripheral hospitals, and this has never happened in my 39 years in this hospital. We took nonveterans here because one of the VA's missions is to back up the community. There were patients coming from Elmhurst Hospital, which was hit very badly in the middle of Queens. That was kind of the epicenter of the epicenter."

Fishbane and Radhakrishnan said that a key part of staffing was having someone who could take the time to coordinate care. Radhakrishnan participated in daily video conference calls among his institution's various campuses to discuss who had the most patients, and whether there was a need to move machines and supplies among hospitals. "The hospital was very gracious in supplying a coordinator who was normally an extracorporeal membrane oxygenation coordinator," he said. "She would make sure that everyone in this task force was on the email chain, provide updates, and ensure that specific tasks were assigned to one or more of the members so they would be completed before the next call. She kept the whole operation together."

Fishbane cited the importance of having someone to provide the "situational awareness at the start of every day—of understanding, I've got this number of patients who are on dialysis, I've got this many machines, this many dialysis nurses and nephrologists. So how is this going to work? It is important having somebody who you can pull back a little bit to be able to stay aware of your resources and to be able to manage them."

Ready for the future?

Northwell Health's Fishbane said he plans to use the summer to be ready for a potential second wave in the fall. His system purchased 10 new Baxter Prismax machines for CRRT and several Tablos that "we are trying to get a lot of experience on. Better to do training when things are slower and people have time to think," he said.

There is general agreement that the experience in responding to the crisis in New York left the U.S better prepared to deal with future large COVID-19 outbreaks—if only because the kidney impacts are now known and can be anticipated. The reserves and supplies of renal replacement therapy equipment are larger, in both government and manufacturer hands.

"We stepped up manufacturing of equipment and dialysis solutions, so we now have an even more robust supply chain in place in case of future spikes," said Fresenius' Turk.

Columbia's Radhakrishnan said: "We are prepared. We have means to deal with it in the future, as long as it doesn't exceed the numbers that we saw."

ASN's Kliger would like to see a better international plan and cooperation, which would avoid hoarding by states and countries and provide for more efficient distribution of supplies and equipment. "In March, equipment and supplies needed to be directed to Italy and Spain. In April things needed to be directed to New York. And maybe next month, they'll need to go to Florida and Arizona," Kliger said. "We need a much more thoughtful global approach of how to deal with pandemics and how to deal with urgent needs that make requirements go up fivefold all of a sudden in one place or another. The answer isn't to say to everybody, well, you better think about this and be prepared for emergencies [because that leads] to nothing but hoarding and inefficient use of equipment." ■

New England Journal of Medicine Retracts COVID-19 Study

The *New England Journal of Medicine* has retracted one of the articles cited in the June *Kidney News* article, "Evidence Mounts that RAS-Blocking Medications Pose No Danger to COVID-19."

The *Kidney News* article described this retracted article as "a database study of 8910 [COVID-19] patients who had been hospitalized in 11 countries on three continents. That study found that neither ACE inhibitors nor ARBs were associated with an increased risk of in-hospital death."

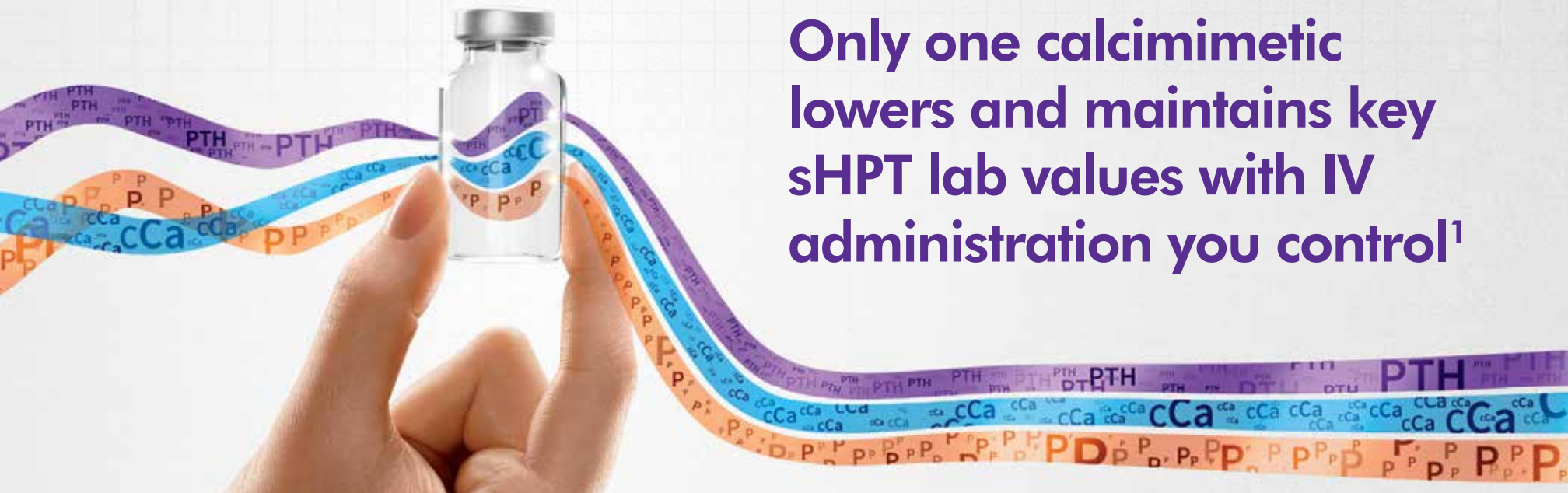
The retraction of this one article does not materially affect the *KN* article's conclusion citing an expert consensus that patients on blood pressure medications that block the renin-angiotensin system should continue taking these drugs during the COVID-19 pandemic unless otherwise instructed by a physician.

The study's authors wrote that the retraction was necessary, stating that "because all the authors were not granted access to the raw data and the raw data could not be made available to a third-party auditor, we are unable to validate the primary data sources underlying our article."

The *Lancet* also retracted a paper from the same lead author, Mandeep R. Mehra, MD. The *Lancet* paper received a great deal of attention because it found no benefit in the use of hydroxychloroquine or chloroquine to treat COVID-19.

In both cases, the problems related to the use of a database provided by Surgisphere Corp. Surgisphere declined to release the full dataset to independent peer reviewers because a transfer "would violate client agreements and confidentiality requirement," according to the retraction statement in the *Lancet*.

"I did not do enough to ensure that the data source was appropriate for this use," Mehra said in a statement apologizing for the "disruptions" the papers caused. ■



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.

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.

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.

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/

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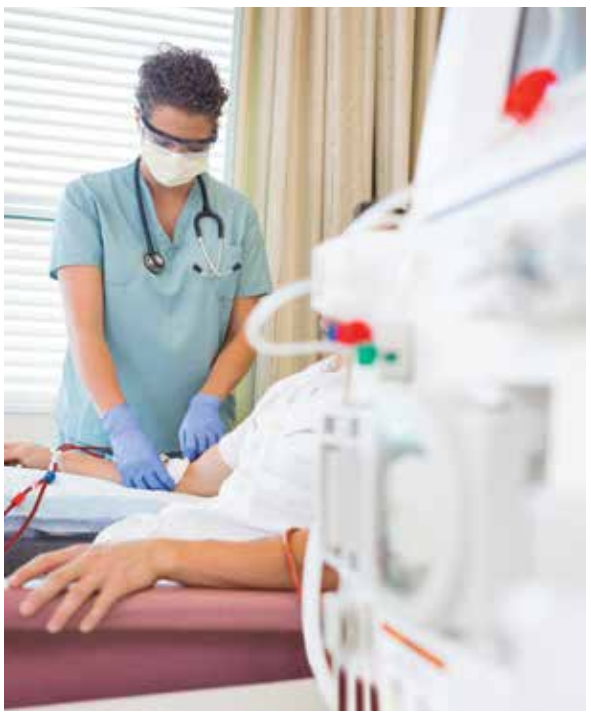
Policy Update

ASN has recently advocated for numerous policies that address the current kidney care system as well as the effects of COVID-19 on kidney patients and kidney care professionals.

COVID-19

The COVID-19 pandemic has posed unique challenges for the 37 million Americans affected by kidney disease and the physicians who care for them as parts of the nation transition to various phases of reopening. ASN recently collaborated with the National Kidney Foundation (NKF) on behalf of kidney patients and kidney care professionals in advocacy efforts on two COVID-19 related policies.



Discriminatory Ventilator Policies

COVID-19 has created challenges for states and hospital systems that face limited medical resources, including ventilators. Blanket crisis-management policies that were previously developed or under consideration by states and hospital systems arbitrarily deprived certain patients, including kidney patients, of life-saving interventions, such as ventilation.

ASN and NKF wrote to both the National Governors Association and the National Conference of State Legislatures requesting that they urge their members to ensure their states, and the healthcare systems therein, to not tolerate this type of discrimination.

ASN also alerted the Department of Health and Human Services (HHS) of potentially discriminatory policies, specifically flagging those concerning kidney patients. The HHS Office for Civil Rights (OCR) recently took enforcement measures against states with discriminatory ventilator rationing guidelines. OCR also collaborated with the Federal Emergency Management Administration/HHS Healthcare Resilience Task Force to release official Crisis Standards of Care and Civil Rights Laws guidance for resource-constrained settings.

The OCR guidelines are available on HHS.gov, and ASN members are encouraged to file a complaint with the HHS Office for Civil Rights if they encounter instances of discriminatory policies or resistance to the policies outlined in the guidance.

Reopening the Nation Safely

While the COVID-19 pandemic has begun to slowly subside in portions of the country, HHS is beginning to consider and establish guidelines to reopen the nation. ASN and NKF sent a list of policy recommendations to HHS Secretary Alex Azar for consideration. These recommendations urge the administration to consider the unique needs of kidney patients, who are particularly vulnerable to COVID-19 infection, and the kidney care professionals who care for them as the country reopens.

In the letter, ASN and NKF encourage the administration to adopt policies and procedures "to ensure kidney patients, their families, and clinicians have adequate access to personal protective equipment, priority access to COVID-19 testing, and early access to a vaccine once it is developed; support end stage renal disease (ESRD) patients' ability to safely access dialysis services and other related care; prioritize the safe resumption of organ transplantation, which has significantly declined as a result of COVID-19; extend and build upon temporary policy changes that may be required to meet the ongoing needs of kidney patients; and address the needs of patients who develop acute kidney injury (AKI) as a result of COVID-19 infection."

CMS Regulations on AKI and Peritoneal Dialysis

As reported in the article in this issue, "More Than One-Third of Hospitalized COVID-19 Patients Develop AKI, Study Finds," the scope of AKI associated with patients hospitalized with COVID-19 is just beginning to be understood and more widely reported. Many of these AKI patients were started in hospital with peritoneal dialysis (PD). Currently, CMS regulations do not allow in-center dialysis facilities to perform PD nor do they allow AKI PD patients to be discharged directly to home. This has complicated care for these patients, often necessitating that they undergo another procedure to switch to hemodialysis. ASN is working with CMS to address this issue in upcoming rulemaking this summer.

NIDDK Replaces Parent T32 Program

In April 2020, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) published two notices (NOT-DK-20-023, NOT-DK-20-024) announcing that the Division of Kidney, Urologic, & Hematologic Diseases (KUH) will no longer participate in the traditional National Institutes of Health (NIH) National Research Service Award (NRSA) T32 Program and instead will participate in a new Institutional Training Program.

This abrupt announcement came as many programs were in the process of completing competitive renewals and will significantly impact the programs currently funded under the T32 mechanism.

Given the gravity and consequences of these unexpected changes, a large number of ASN's more than 21,000 members contacted the society to articulate their concerns regarding NIDDK's announcement. The ASN Policy and Advocacy Committee discussed these concerns, identified approaches to address them, and asked the ASN Council to submit these recommendations to NIDDK and KUH. ASN recommended that NIDDK consider the following:

- Providing bridge funding to programs that were/are in the process of competitive renewals to the Parent T32. This funding is necessary in enabling the transition for many programs, especially those that have already identified fellows.
- Articulating its rationale for limiting the number of eligible programs to fewer, larger Institutional Network Awards given the T32 program's historical success and that they provide more research training opportunities for individuals than the announced Institutional Network Award.
- Giving ASN an opportunity to provide further input to NIDDK as the institute drafts the Funding Opportunity Announcement to invite applications for Institutional Network Awards for Research Training. (ASN's offer to serve as a resource to NIDDK on this issue was not accepted.)

More than a month after its initial announcement, NIDDK on May 28, 2020, published a Funding Opportunity Announcement for the "Institutional Network Awards for Research Training" (PA-20-220), the new program that will be in lieu of KUH's participation in the traditional Parent T32.

The new program has fewer, but larger, Institutional Network Awards (U2C/TL1) and, in an attempt to foster a community of trainees, NIDDK has limited applicant organizations to submitting only one Institutional Network Award application that spans kidney, urology, and hematology training at the institution. KUH and NIDDK also encourage "a single, consolidated application from several institutions within the same metropolitan area that include multiple departments with a different research focus" supporting at least five trainees across kidney, urologic, and hematologic research areas through the award. The new program seems to favor larger institutions with existing training programs that have at least two foci that include kidney, urologic, or hematologic research.

ASN believes the new program's focus on fewer but larger awards will lead to the exclusion of many worthy institutions from the research process, while also exacerbating the declining ranks of successful scientists in nephrology and the recruitment of more junior scientists.

With some current T32s in metropolitan areas ending at different times, ASN is concerned that these institutions will inadvertently receive an advantage in the application process for the new Institutional Network Award. Smaller programs that end sooner, in 2020 or 2021, will be at a significant disadvantage in the application process for the Institutional Network Award. There is no incentive for current T32 programs that end in 2022, 2023, or 2024 to consider joining with those that end in 2020 or 2021 to strengthen the application, so smaller programs that end sooner will face a considerable setback before the application process begins.

Finally, ASN members and the kidney community overall have been stretched thin while addressing the current COVID-19 public health emergency, particularly those in major metropolitan areas or areas highly impacted by COVID-19. The sudden timing of NIDDK's announcement in April 2020, which was just weeks away from the T32 submission deadline for competitive renewals for which many programs were in the midst of applying, placed another burden on the kidney community. ASN believes that the application window for the new Institutional Network Award does not consider the community's current circumstances.

NIDDK announced that it would hold a webinar in anticipation of many questions from the community about the Institutional Network Awards, but as of press time, the webinar had not occurred.

Extending Immunosuppressive Drug Coverage

ASN is collaborating with the broader kidney and transplant communities in advocacy efforts to pass the bipartisan Comprehensive Immunosuppressive Drug Coverage for Kidney Transplant Patients Act (H.R. 5534/S. 3353).

Currently, Medicare only covers immunosuppressive medications for three years after transplantation. Transplant patients who lose Medicare coverage and are no longer able to access vital immunosuppressive medications are at risk of losing their transplant and returning to dialysis.

The Comprehensive Immunosuppressive Drug Cov-

erage for Kidney Transplant Patients Act would permanently remove the three-year limit from Medicare, extend Medicare's coverage of immunosuppressive medications beyond the current limit when the individual has no other coverage, and ultimately save lives.

The Department of Health and Human Services has predicted that extending Medicare's coverage of immunosuppressive medication would also result in significant savings to Medicare by diverting patients from costly dialysis—a treatment that is 300% more expensive.

ASN will continue to advocate for the legislation's passage on behalf of the more than 700,000 Americans with kidney failure and continue to provide updates to the ASN membership.

Medicare Advantage

In a letter to Administrator Seema Verma of the Centers for Medicare & Medicaid Services (CMS) last month, ASN expressed its support for Medicare Advantage (MA) expanding access to allow patients with kidney failure to enroll in MA beginning in January 2021. These expanded plans can enable patients to access more choices and additional benefits such as transportation assistance, greater care coordination, or even dental care.

In the MA final rule, CMS took several steps affecting network adequacy in MA plans with some provisions potentially affecting kidney care coverage. The step that has drawn the most attention in the kidney community is CMS' decision to not include maximum time and distance standards for outpatient dialysis to achieve network adequacy in MA plans.

ASN had supported CMS' bold language in the proposed rule to reconsider how to achieve network adequacy allowing for the inclusion of innovation in care delivery, increased use of telehealth, and home dialysis. However, the step to totally and immediately remove these in-center facilities from those requirements in MA plans did surprise many.

Members of the kidney community and ASN are voicing some concerns that this step could have unintended consequences that affect dialysis patients. Patients utilizing home dialysis are sometimes transitioned to in-center hemodialysis or need access to in-center facilities for a limited period of time. In such cases, there is concern that patients may not be able to see their nephrologist, could face higher out-of-network costs under a MA plan, and could have a substantial transportation burden.

Highlighting these concerns to CMS, ASN urged the agency to use its authority to maintain safety guardrails for patients and ensure the transparency needed to guarantee greater patient access to MA plans. ASN also urged that CMS continue to uphold existing policy to allow for equal access to healthcare choices, including the following: *Ensuring access to all necessary dialysis care (including in-center care) in accordance with community standards of care (recognizing that the community standard of care in San Ysidro, New Mexico, may look substantially different than the community standard of care in San Francisco, California, for example).*

ASN also encouraged CMS to aggressively use the Medicare Office of the Ombudsman to not approve plans constructed to avoid geographic areas with higher concentrations of Medicare/Medicaid dual eligible, and that reliance on hospital-based dialysis care only is not an acceptable substitute for meeting community standards of care for in-center hemodialysis.

To best evaluate the MA plans, ASN urges patients considering MA to review the healthcare professionals and dialysis organizations included in the available MA plans' in-network coverage. ■

More Than One-Third of Hospitalized COVID-19 Patients Develop AKI, Study Finds

By Bridget M. Kuehn

More than one-third of patients hospitalized for COVID-19 in a large metropolitan New York heath system developed acute kidney injury (AKI), according to a study published in *Kidney International* (1).

The largest study to date on the incidence of AKI in the United States, the study included 5449 adults admitted with COVID-19 to one of 13 hospitals in the Northwell Health system and found that 36.6% of the patients experienced a kidney injury. There was also a strong relationship between kidney injury and respiratory failure, noted study co-author Jia Hwei Ng, MD, Assistant Professor of Medicine at the Zucker School of Medicine at Hofstra University Northwell Health in Great Neck, New York. About 90% of patients who required mechanical ventilation developed AKI and most of these injuries happened within a day of intubation.

"This gives us some insight that as soon as the patient is admitted with COVID, we have to watch really closely," Ng said. She also recommended taking note of their volume status and not being afraid to give fluid. Furthermore, many patients with AKI had lower volumes based on urine data, possibly because many had already had fevers for several days. Patients taking vasopressor medications were also at higher risk of kidney injuries.

Daniel Batlle, MD, the Earle, del Greco, Levin Professor of Nephrology/Hypertension at Northwestern University Feinberg School of Medicine in Chicago, said the study may be the best data available to date on the incidence of AKI in COVID-19 patients.

"The key thing about this paper is the temporal relationship, how quickly you see AKI when the patient goes to the intensive care unit (ICU) for intubation and the use of the respirator," said Batlle, who was not involved in the study.

Kidney injuries are very common in ICU patients, but in COVID-19 patients they seem to be happening faster, Batlle said. In an observation that may boost understanding of potential mechanisms, Ng noted that the kidney damage appears to be caused by tubular injuries as a result of a loss of blood flow. Batlle and colleagues recently described what appears to be a multifactorial mechanism of AKI in patients with COVID-19 (2).

"It looks like this type of AKI is not the bread-and-butter AKI we see all the time," Batlle said. In particular, he highlighted the high rate of blood clot formation and the need to give anticlotting agents to patients who require renal replacement.

The study also suggests a much higher incidence of AKI in hospitalized COVID-19 patients than previous studies, which have found rates as low as 5% in China (3) and 19% in Seattle (4), Ng said. A likely reason for the higher rate of kidney injury was that the patients included in this study had more comorbidities and were more likely to need mechanical ventilation than in other studies, Ng said.

The researchers also found that 14.3% of these patients required renal replacement therapy.

They expected a higher rate of AKI than previous studies based on what they were seeing in New York, said study co-author Kenar Jhaveri, MD, associate chief of the division of kidney diseases and hypertension at the Zucker School of Medicine at Hofstra University Northwell Health. "We expected the incidence to be at least above 20%," he said. "What was surprising to us was that almost 15% of those with AKI ended up needing dialysis, or 5% [of all COVID-19 inpatients] needed dialysis. That was a little bit shocking."

Like many health systems in New York and other hard-hit areas of the country, Northwell experienced a surge in demand for dialysis (5). The system had begun planning about a month before the surge and purchased more dialysis equipment and dialysis fluid. "We were on edge," as patients started arriving, Jhaveri said. By moving supplies among the system's 23 hospitals as needed they were able to keep up. But keeping up adequate staffing levels of nurses trained in dialysis was difficult, especially when some nurses became sick.

"We really had to make sure we had enough nursing staff and physician staff to take care of these patients," Jhaveri said. "That was the biggest challenge."

Jhaveri said he hoped the data would help hospitals prepare for potential future surges of coronavirus patients.

"If they know these numbers to get a better sense, okay, so if 35% get injuries, maybe we should add additional kidney doctors in the hospital instead of being in the office so that there's enough manpower, so people don't get burned out," he said. "That's where this is going to be very useful, in planning."

Ng and Jhaveri plan to do further analyses of the patient data after 60 days, which may provide more insights about recovery rates from coronavirus-associated kidney injuries. Such longer-term data will be important to see how the condition evolves and how many patients recover, Batlle said.

The study was funded by the Feinstein Institutes for Medical Research at Northwell Health.

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Buttonhole Cannulation of Arteriovenous Fistulas

A Prickly Problem

By Michele H. Mokrzycki

Infection rates associated with native arteriovenous fistulas (AVFs) are low compared with arteriovenous grafts and tunneled hemodialysis (HD) catheters (1). However, the type of AVF cannulation technique has a significant impact on subsequent infectious complications. The "buttonhole" (BH) or "constant site" AVF cannulation technique refers to the insertion of blunt needles through two developed fibrous tunnels/tracts at consecutive dialysis treatments.

The two alternative AVF cannulation techniques are the "rope-ladder" (RL) technique, which involves using a different site to place two sharp needles during consecutive HD sessions, and the "area" or "cluster" technique, in which sharp needles are placed in the same general area (Figure 1) (2). All three techniques have been used for AVF cannulation in both the in-center and home HD settings. In comparison with standard cannulation (SC) techniques, BH cannulation requires weeks of development of both tracts, the use of blunt needles once fibrous tunnels are formed, special training for cannulators, and additional time required for and attention to important steps for disinfection before and after the scab is soaked for gentle removal before cannulation, and application of mupirocin ointment after decannulation (2–4). The buttonhole technique was first introduced for the cannulation of AVFs with short segments, and initial series reported less pain and fewer infiltrations or hematomas because the blunt needles caused less trauma (5, 6).

International data from Canada, Australia, Denmark, and Belgium report a significantly higher infection rate with use of the BH technique. In a randomized controlled trial comparing BH with SC in 140 in-center HD patients in Alberta, Canada, who were followed up over a long term, there were 12 infections in the BH group, including nine episodes of *Staphylococcus aureus* bacteremia, whereas there were zero infections in the SC group (incidence rate ratio 63.29; 95% confidence interval 22.2–180; $p < 0.001$) (3). Although fewer patients who underwent BH needling experienced a hematoma, there was no difference in pain, AVF thrombosis, interventions, or survival (7, 8).

In a retrospective review of BH cannulation in 90 home HD patients at an Australian center, the total infection rate was nearly fourfold higher in patients using BH needling than in those using the RL technique (9). A quality improvement initiative, introduced for patients using BH needling at an in-center HD facility in Belgium, reported a reduction in the incidence of total infectious events (from 0.43 to 0.34 per 1000 AVF days); however, the incidence was still twofold higher with BH than with RL (0.34 vs. 0.17 per 1000 AVF days; $p = 0.003$) (3). In that study, the BH technique was associated with a significantly higher incidence of *Staphylococcus aureus* and *S. epidermidis* bacteremia, metastatic infections, and deaths. Similarly, a single-center study from Ontario, Canada, reported significantly higher rates of *S. aureus* bacteremia with metastatic complications in a home HD patient population using BH cannulation. After the introduction of topical mupirocin, the rate of *S. aureus* bacteremia improved significantly (0.23 vs. 0.03 per 1000 AVF days). The risk for the development of *S. aureus* bacteremia in the observation period, before the introduction of a topical mupirocin protocol, was sixfold higher than in the period after routine use of mupirocin prophylaxis (odds ratio 6.4; 95% confidence interval 1.3–32.3; $p = 0.02$) (4).

There was great interest in the safety of the BH technique for AVF cannulation in a recent online conversation on the Nephrologists Transforming Dialysis Safety (NTDS) ASN Communities website. The ASN Communities post was initiated by Valerie Luyckx, MBBCh, from Brigham and Women's Hospital in Boston, Massachusetts, who raised a concern that patients using the buttonhole technique might become "transiently bacteremic more commonly than we may realize" and identified the need for a prospective study. The responses and opinions have been quite extreme and range from "buttonhole cannulation should be abandoned" to "buttonhole should not be taken off the table for home HD patients." Peggy Bushey, RN, from the home hemodialysis program at the University of Vermont Medical Center, shared a successful antiseptic protocol for buttonhole cannulation in home HD patients where cannulators are limited to one skilled person: the patient or the caregiver. Unfortunately, the buttonhole technique was terminated in the in-center HD setting at this facility because of an increase in infections. Potential reasons given for this finding were the use of multiple AVF cannulators with varied skill levels and the time demands in a busy in-center HD facility.

In a recent *Kidney360* article, the United States experience with buttonhole AVF cannulation was reviewed by Tushar Vachharajani, MD, and col-

When the buttonhole AVF cannulation technique is used, it is critical that strict aseptic technique is followed and that a topical antibiotic, preferably mupirocin, be used after decannulation.

Table 1. Buttonhole arteriovenous cannulation outcomes reported by individual US hemodialysis centers

Reference	Year	Study design	N	BH Infections	BH infiltrations	Access patency	AVF aneurysms
Ball(10) 4 HD centers	2007	Case control	BH 25/RL 17	Similar	Lower	Similar	None
		Survey	Total 61	Lower	Lower	NA	NA
		Case series	BH 13	8%	NA	NA	NA
		Case series	BH 14	21%	NA	NA	NA
Pergolotti (11)	2011	Case series	BH 21/RL24	NA	NA	NA	BH 20%/ RL46%
Birchenough (12)	2010	Pre- and post-QI initiative	NA	BH 52%/RL 5%			
BH30%/RL NA	NA	NA	NA				
Chan (13)	2014	Case series	BH 45/RL 38	BH 11%/RL 8%	NA	Similar	NA
Moore (14)	2019	Case series	BH 14	1 local infection	NA	NA	NA

Abbreviations: AVF = arteriovenous fistula; BH = buttonhole; NA = not available; QI = quality improvement; RL = rope ladder. Adapted with permission from Vachharajani et al. (2).

leagues from the NTDS Vascular Access Workgroup (2). The BH data for the HD patient population in the United States are not as robust as the international data (Table 1) (10–13). Most of the available data from the United States on this topic are derived from small single-center cohorts. The follow-up periods are relatively short, and the outcomes not well defined according to standard criteria.

A single-center study from New York, which included both in-center and home HD patients, reported the experience before and after the introduction of a quality improvement initiative for BH cannulation. Although the quality improvement initiative was associated with a reduction in BH-associated vascular access infections from 50% to 30%, the BH infection risk was still substantially greater than that associated with the RL technique at 8% (12). The largest BH study in the United States was performed by Lyman et al. (15) This was a retrospective observational analysis using data from the National Healthcare Safety Network (NHSN) surveillance report from 2013 to 2014. In 2014, 9% (n = 271,980) of all AVF patient-months reported to NHSN were among BH patients. After adjustment for facility characteristics and practices, BH cannulation was associated with a 2.5-fold higher risk of an access-related bloodstream infection and a 1.5-fold greater risk of a local access site infection in comparison with SC.

The most recent vascular access guidelines from the National Kidney Foundation Kidney Disease Outcome Quality Initiative recommend that BH cannulation be limited to special circumstances, given the associated increased risks of infection and related adverse consequences (16). The guidelines were presented at the spring clinical meetings in May 2019. In my opinion, this recommendation is appropriately prudent. When the BH AVF cannulation technique is used, it is critical that strict aseptic technique is followed and that a topical antibiotic, preferably mupirocin, be used after decannulation. The *Kidney360* review by Vachharajani et al. (2) provides evidence-based protocols for BH cannulation (Figures 2 and 3). ■

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Figure 1. Arteriovenous cannulation techniques

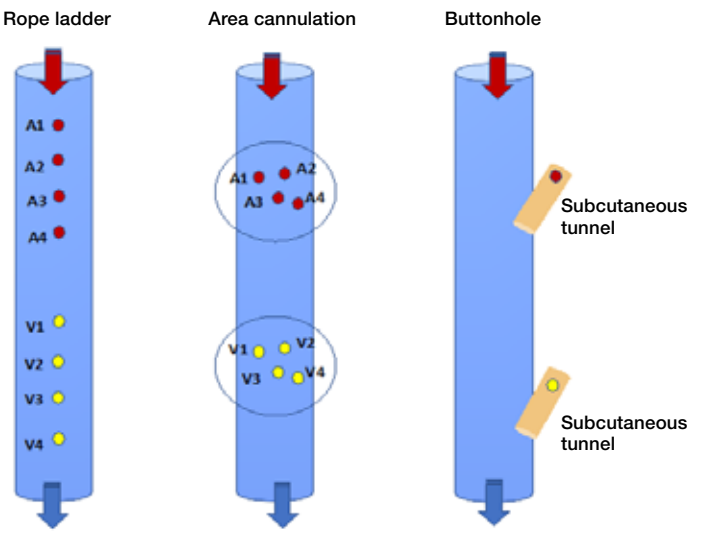

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Figure 2. Protocol for antiseptic arteriovenous fistula cannulation when the buttonhole technique is used

Reprinted with permission from Vachharajani et al. (2).

Figure 3. Recommended antiseptic protocol for arteriovenous decannulation when the buttonhole technique is used

Reprinted with permission from Vachharajani et al. (2).

This article is the first in a series about peritoneal dialysis. Additional articles will be published in upcoming issues.

History of Adequacy Trials in Peritoneal Dialysis

By Ankur Shah and Natasha Dave

In the day-to-day jargon of a nephrologist, the word "adequacy" is unique in its usage in this profession. Whereas the Merriam-Webster definition of "adequate" is "sufficient for a specific need or requirement," nephrologists use this term to reflect the quality of the dialysis prescription.

Measuring the adequacy of hemodialysis (HD) and peritoneal dialysis (PD) has long been a topic of intense interest and debate. Currently, we measure adequacy using the fractional urea clearance equation known as Kt/V, whereby K is the clearance of urea, t is time during dialysis, and V is volume of distribution of urea.

Over three decades, the goal Kt/V range has evolved from a numeric value to a patient-centric approach. The initial recommendation of total Kt/V of 2.0 and total creatinine clearance of 60 L/week per 1.73 m^2 was made by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) in 1997 (1). Later, between 2005 and 2006, both the International Society for Peritoneal Dialysis (ISPD) and the KDOQI recommended a total kidney and peritoneal Kt/V of 1.7 (2, 3). The most recent ISPD guideline update, made in January 2020, now recommends against treating to a specific Kt/V (4). To understand the evolution of Kt/V recommendations, it is imperative to review the history of adequacy trials (Figure 1).

One of the first large trials to evaluate PD adequacy was a prospective observational cohort study, "Adequacy of Dialysis and Nutrition in Continuous Peritoneal Dialysis: Association with Clinical Outcomes," also known as the CANUSA trial (5). From 1990 to 1993, 680 patients using continuous ambulatory peritoneal dialysis (CAPD) were enrolled in Canada and the United States to evaluate the relationship of dialysis adequacy and nutritional status to mortality, morbidity, and technique failure. The analysis of this study led to the target weekly Kt/V of 2.0 for patients using CAPD. In addition, every 0.1 decrease of Kt/V resulted in an increased risk of death by 5%. These findings assumed that PD clearances and residual kidney function were equivalent and therefore additive (5). Years later, a repeated analysis was done to address this assumption and revealed that there was no association between increased peritoneal creatinine clearance and risk of death; instead, the mortality benefit was due to residual kidney function, not to increased dialysis dose (6).

Independently in 1999, the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) considered patient-reported outcomes in the context of delivered dialysis dose (7). This study showed that PD symptom burden was not caused by dialysis dose; rather, it was affected by low residual GFR (rGFR), lower percentage of lean body mass, and past episodes of underhydration. Later, in 2003, the same group evaluated the significance of rGFR and PD clearance in relation to patient survival and quality of life. This was a prospective cohort study of 413 incident PD patients in the Netherlands and was known as NECOSAD-2. The result revealed that for every milliliter per minute of rGFR, there was a relative decrease in mortality of 12%; furthermore, no significant effect of PD clearance on mortality was found. The combined findings of CANUSA and NECOSAD-2 inspired others to conduct randomized controlled trials evaluating this association (Table 1).

In 2002, a prospective randomized controlled trail in Mexico, the ADEMEX trial, sought to study the effects of increased peritoneal clearances on mortality rates in PD (8). This study randomized 965 patients to receive four daily 2-L exchanges or to be dosed to achieve a peritoneal creatinine clearance of >60 L/week per 1.73 m^2, through either increased volumes or exchanges. The average Kt/V of the intervention group was 2.27, and that of the control group was 1.8. At 2 years, the percentage of survival was no different between treatment groups. Predictors of patient survival in this trial included age, presence of diabetes, albumin concentration, and residual kidney function. Several secondary outcomes were also evaluated; only serum albumin and total peritoneal ultrafiltration were significantly higher in the intervention group. Despite the higher serum albumin in that group, the change from baseline was not statistically significantly different. Hospitalization rates were also similar for both groups in both unadjusted and adjusted analyses.

One year later, Lo et al. (9) published the results of the Hong Kong study, another randomized controlled trial of adequacy in the CAPD population. Enrolled incident CAPD patients (n = 320) were randomized to three groups: Kt/V 1.5–1.7, Kt/V 1.7–2.0, and Kt/V >2.0. Of note, only peritoneal clearance, not residual kidney function, contributed to the difference in Kt/V. The results showed no difference in survival among any of the groups; however, there was a significantly higher dropout in the group achieving Kt/V 1.5–1.7, as a result of hypervolemia, uremia, and worse anemia.

Both the ADEMEX trial and the Hong Kong study helped pave the way to re-address previous adequacy goals in patients using PD. In 2005 the ISPD and in 2006 KDOQI endorsed a weekly Kt/V target of 1.7 (2, 3). Additionally, if patients are reliant on residual kidney function, or rGFR, to achieve adequacy, those guidelines recommend frequent monitoring of 24-hour creatinine clearance (every 1–2 months).

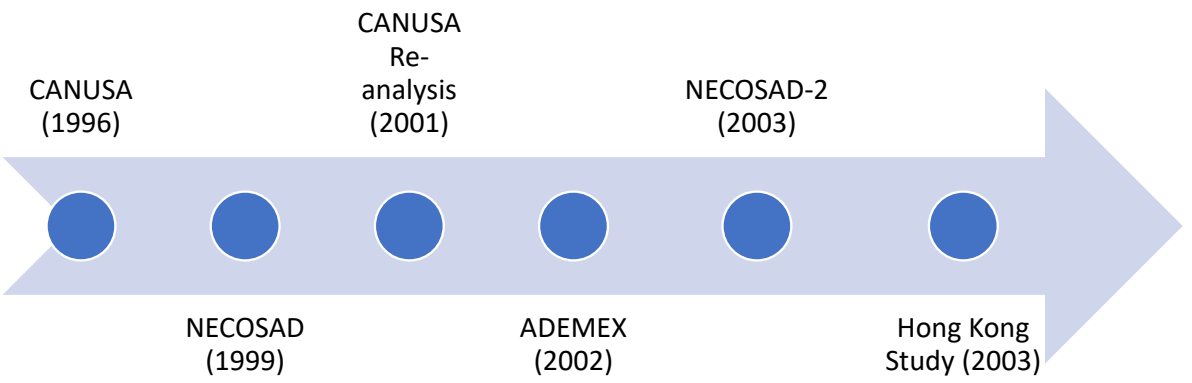
In the context of these recommendations, it is important to note that the concept of adequate dialysis is, of course, not limited to a single solute. Assessments of adequacy should consider quality of life, volume status, nutrition, eukalemia, acid–base disturbances, and uremic symptoms. The quantity of delivered dialysis should be adjusted regardless of Kt/V for patients in whom the above factors are not controlled. This can be achieved by increasing dwell volume, changing dwell time, or adding exchanges (4).

Among other considerations nephrologists must take into account are the implications of increased clearance on the patient. Increasing clearance requires the use of additional dialysate, which increases the risk for hyperglycemia and for advanced glycosylation end products, and also increases the risk for complications associated with blood pressure and volume. Furthermore, additional clearance may require manual exchanges, which may affect quality of life. Reduction of PD clearance minimizes these risks for patients and can improve patient-reported outcomes (4).

Congruous with a more comprehensive approach to dialysis adequacy, the ISPD has released 2020 guidelines recommending against a specific Kt/V goal. Instead, the ISPD advocates for a more holistic approach, including close monitoring of patient-reported outcome measures, fluid status, nutritional status, and toxin removal (4).

Over the past few decades, the recommendations for PD adequacy have evolved from numeric targets to a comprehensive assessment. The initial shift toward less stringent guidelines resulted from two randomized controlled

Figure 1. Landmark trials in peritoneal dialysis



Abbreviations: ADEMEX = ADEquacy of PD in MEXico; CANUSA = Canada-USA; NECOSAD = Netherlands Cooperative Study on the Adequacy of Dialysis

Table 1. Summary of randomized controlled trials assessing adequacy in peritoneal dialysis

Trial	Population	Intervention	Comparison	Outcome
ADEMEX (RCT)	Enrolled 965 incident and prevalent PD patients	Peritoneal creatinine clearance of 60 L/wk per 1.73 m^2	Preexisting PD prescriptions (this is about 45 L/wk or 4 daily 2-L exchanges)	No difference in mortality at 2 years
Hong Kong Study (RCT)	Enrolled 320 incident CAPD patients	Kt/V 1.7–2.0 or Kt/V >2.0	Kt/V 1.5–1.7	No difference in mortality at 2 years, more uremia and volume overload in group with Kt/V of 1.5–1.7

Abbreviations: ADEMEX = ADEquacy of PD in MEXico; CAPD = continuous ambulatory peritoneal dialysis; PD = peritoneal dialysis; RCT = randomized controlled trial.

trials, the ADEMEX trial and the Hong Kong Study. This paved the way for the 2006 KDOQI recommendations for a weekly Kt/V target of 1.7. The 2020 ISPD guidelines have taken this a step further, advocating for a more holistic approach rather than the specific targeting of a single clearance metric. It is imperative for us as nephrologists to understand the evolution of adequacy in PD and the implications of increased clearance in patients using PD. Studying this evolution allows clinicians to be better equipped to understand current practice guidelines while also providing a foundation for the development of future studies. Furthermore, this article highlights the importance of considering the patient in context to the guideline instead of achieving a numeric goal.

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Fellows Corner

@RenalFellow, #NephTwitter Wants YOU

By Tiffany Truong

Tiffany Truong

Love it or hate it, social media has become an ever-pervasive presence in nearly every aspect of our lives, and no sphere has been spared, *especially* nephrology. We may postulate that this is perhaps because nephrology, by its very nature, provides such a rich soil for academic discourse; that fluid physiology demands a blog post, electrolyte puzzles make great tweets, and regardless of all that we just cannot help posting salty jokes. That may be true, but certainly the world of nephrology on social media as we know it has also been laboriously designed through the slow, steady work of the Nephrology Social Media Collective (NSMC), which (disclaimer) I joined as an intern in January 2020. It is my opinion that to know the presence of nephrology in social media is to know the work of the NSMC.

Since 2015, the NSMC has held elaborate annual online events such as NephMadness, hosted journal clubs on Twitter through NephJC, and created an array of other collaborative resources, including Renal Fellow Network and NephSIM. As a nephrology fellow I had known about the programs long before I knew about the creators, and I was a consumer of their content long before I joined nephrology, let alone any discourse on social media. Now, as a first-year fellow, my days on service can be invariably busy and dedicated to patient care, but in those few minutes between clinic and grand rounds or after a hectic day on consultations, I find that some time spared to follow the world of nephrology on social media provides many benefits.

To start, social media can be fun. At first glance, "fun" may sound trivial, but that enjoyment becomes enthusiasm, which can lead to passion, drive, and initiative. In a time when physician burnout is a recurring headline and is being rebranded as "moral injury," remembering that our work is creative, intriguing, and rewarding is arguably as vital as any duty hour regulation. It spills over into patient care. It has been my experience that most physicians who use social media are not there to represent any financial interest; they maintain a presence because being a part of it is gratifying on its own.

Besides the feel-good value, however, the blogs, websites, and Twitter accounts of these nephrologist/social-media-guru pioneers are brimming with educational dialogue that can enrich one's professional growth. There is much to learn, from the tweetorials on physiology to journal clubs on current research to lively debates on how management should or should not change after a study. This virtual community, deemed "NephTwitter," is an academic gathering place for nephrologists around the world, who can share their unique experiences while still speaking in the common tongue of nephrology. One of the most successful social media experts in medicine, Dr. Anthony Breu, has emphasized that social media's major impact is not just the dissemination of information but a shift in the entire clinical perspective from that trap of anchoring: from asking "What is the answer?" to "Why is there a problem?" and "Why does this work?"

The funny thing about online discourse is that it is a great equalizer, particularly for fellows. Although we are all identified professionally, the hierarchy of attendings, fellows, residents, and students does not translate into rigid roles. We are all simply teachers and students, with things to say and things to learn.

Last but not least, social media is an avenue for patient advocacy. The American Medical Association and other professional societies, notably in pediatrics, agree that physicians have a responsibility to advocate for public health and address the root causes of threats to the public well-being. Although civic engagement among physicians is easily touted, many of us have no formal training to advocate for healthcare beyond our individual patients. In a field as institutionalized as nephrology, this is remarkable. Social media provides a platform, accessible to everybody, that if used judiciously can inform our patients and our communities about even the sociopolitical barriers to health that we know intimately.

In the Netflix show *Diagnosis*, Dr. Lisa Sanders uses the web to connect patients with difficult diagnoses to experts across the world. She states, "One of the tools that doctors use are the other doctors in the room. . .what we're doing is just making the room that much bigger." To be a nephrology fellow in this day and age is to train in an enormous room, one with very smart little blue Twitter birds who spout Free Open Access Medical education (FOAMed). That is the sound of the NephTwitterverse calling. Consider yourself recruited. ■

Tiffany Truong, DO, is a nephrology fellow at the University of Southern California.

Preventive drug lists lead to increased use of essential medications for diabetes

For diabetic patients in high-deductible health plans (HDHPs), the introduction of preventive drug lists (PDLs)—with no copayments for preventive medications—is associated with lower out-of-pocket costs and increased use of essential medications, reports a study in *Medical Care*.

The researchers evaluated a natural experiment using data on commercially insured patients with diabetes enrolled in HDHPs (individual deductible at least $1000) linked to health savings accounts. Approximately 1750 patients in an intervention group were switched by their employers to PDL coverage. This meant that essential medications and supplies for preventing adverse outcomes of diabetes—including antidiabetic drugs, insulin, test strips, and blood pressure-lowering and cholesterol-lowering drugs—became available with no or limited cost sharing.

Patients switched to PDL coverage were propensity-matched to a control group of approximately 3350 patients enrolled in HDHPs with no PDL. Out-of-pocket costs for medications were compared between groups. Medication use was assessed in terms of pharmacy fills, converted to 30-day equivalents.

Patients who transitioned to PDLs saw a significant decrease in medication costs. The average saving was $621 per member per year: a 35% reduction. The reduction in out-of-pocket costs was associated with a sharp increase in the use of preventive medications: six additional refills per year, on average.

The increase in medication use was more than twice as large for lower-income patients: 6.6 refills per year, compared with 3.0 for higher-income patients. "Overall savings in out-of-pocket spending were much larger for patients with severe diabetes, primarily due to savings on insulin," the researchers note.

A growing number of Americans are enrolled in HDHPs, with the goal of reducing unnecessary care while promoting higher-value care. However, deductibles, copayments, and other forms of cost sharing can adversely affect the use of needed medications for chronic diseases, including diabetes. To address this issue, some employers and insurers have introduced PDLs, exempting specific medications from deductibles and copayments.

The introduction of PDLs is associated with lower out-of-pocket costs for people with diabetes in HDHPs, leading to increased use of clinically essential medications. The increases in medication use appear "larger and potentially more important" in lower-income patients. The study appears as part of a special supplement to *Medical Care*, presenting new reports from the Natural Experiments for Translation in Diabetes 2.0 (NEXT-D2) Network [Ross-Degnan D, et al. Reduced cost-sharing for preventive drugs preferentially benefits low-income patients with diabetes in high deductible health plans with health savings accounts: A Natural Experiments for Translation in Diabetes (NEXT-D2) study. *Med Care* doi: 10.1097/MLR.0000000000001295]. ■

Among OPOs, wide variations in kidney procurement costs

The average cost of procuring a deceased-donor kidney is $36,000, but the cost varies substantially between different organ procurement organizations (OPOs), concludes a study in the *American Journal of Transplantation*.

The researchers analyzed annual cost reports from 51 of 58 OPOs in the United States from 2013 to 2017. Data analysis focused on variations in kidney procurement costs, including differences in costs by OPO size, based on annual number of kidneys procured. The analysis also considered costs associated with acquisition of viable (transplanted) versus nonviable (discarded) kidneys and other OPO outcomes.

Over the 5-year period studied, the average cost per transplanted kidney was $36,000 (range, ~$24,000 to $56,000). The average number of kidneys transplanted was 274 per OPO, and the average nonviable kidney rate was 18.4%. The number of nonviable kidneys was positively associated with the number of viable kidneys procured: for every 10 viable kidneys, 2.4 nonviable kidneys would be expected.

The costs per viable kidney were higher for OPOs that procured higher numbers of nonviable kidneys: for a 1% increase in nonviable kidneys, the cost per viable kidney increased by $275. Across OPOs, the cost per viable kidney tended to decrease up to 549 kidneys per year but then increased thereafter. The costs of kidney procurement were also related to local cost levels, donation after cardiac death, year, and standardized donor rate ratio. During the period studied, costs increased by 3% per year.

Although previous studies have exam-

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ined the costs of the organ transplantation process, less is known about the costs of organ acquisition. The new study documents a significant variation in kidney procurement costs among OPOs.

Procurement costs are affected by the percentage of viable versus nonviable kidneys, OPO size, and a range of other factors. The researchers discuss the implications for addressing possible inefficiencies in the current OPO structure [Held PJ, et al. The cost of procuring deceased donor kidneys: Evidence from OPO cost reports 2013–2017. *Am J Transplant* 2020; 20:1087–1094].

CKD patients have worse outcomes with opioids versus NSAIDs

Among patients with CKD, those taking opioids have a higher rate of adverse outcomes than those taking nonsteroidal anti-inflammatory drugs (NSAIDs), reports a study in the *American Journal of Kidney Diseases*.

Using data from the Chronic Renal Insufficiency Cohort (CRIC), the researchers analyzed the relationship between analgesic use and clinical outcomes in patients with CKD. The analysis included 3939 CRIC participants with CKD not requiring kidney replacement therapy (KRT). The patients reported 30-day analgesic use at annual study visits. At baseline, 9.9% of patients were using opioids and 15.5% were taking NSAIDs.

Adverse outcomes were compared for groups with differing patterns of analgesic use. The analysis focused on four clinical outcomes: kidney failure requiring KRT, a composite of kidney failure with KRT plus a 50% reduction in eGFR, death before development of kidney failure, and number of hospital admissions (without kidney failure) between annual study visits. The median follow-up time was 6.84 years.

Time-updated opioid use was associated with increased risk of all four outcomes of interest: HR 1.4 for the composite outcome, 1.4 for kidney failure requiring KRT, and 1.5 for death; and rate ratio 1.7 for hospitalization, compared with patients not taking opioids. Similar patterns were found on subgroup analysis of patients reporting any use of analgesics other than opioids or NSAIDs or tramadol.

By contrast, for time-updated NSAID use, the associations were smaller and were nonsignificant on subgroup analysis. Some associations varied with patient characteristics, including a significant increase in the composite outcome among black patients taking NSAIDs: HR 1.3. For women and for patients with eGFR <45 mL/min per 1.73 m^2, NSAID use was associated with a lower risk of kidney failure: HR 0.63 and 0.77, respectively.

Pain is a common problem among CKD patients, who have limited safe options for analgesia. There are conflicting recommendations as to the safety of NSAIDs in patients with CKD. Some patients use opioids as a supplement to or replacement for NSAID treatment for pain.

This comparative analysis of CRIC data suggests that opioids are more strongly related to adverse kidney outcomes in patients with CKD, compared with NSAIDs. Associations of NSAIDs with adverse outcomes may be limited to certain subgroups, particularly black patients. The researchers write, "Both classes of agents have recognized risk profiles that are likely amplified in CKD, justifying close consideration of their risk versus benefit" [Zhan M, et al. Association of opioids and nonsteroidal anti-inflammatory drugs with outcomes in CKD: Findings from the CRIC (Chronic Renal Insufficiency Cohort) study. *Am J Kidney Dis* doi: 10.1053/j.ajkd.2019.12.010].

Interview with Young Scientist

Uma D. Alappan

KN Editorial Board member Edgar Lerma, MD, FASN, interviewed pre-med student Uma D. Alappan about her poster at the recent National Kidney Foundation's (NKF) Spring Clinical Meetings. Lerma first interviewed Alappan in 2016 upon her presentation of a poster at ASN Kidney Week.

Uma D. Alappan

Four years ago, I interviewed you for* Kidney News *about your poster at ASN Kidney Week. You were a high school junior at the time. Can you briefly tell us how your research has developed since then?

I will always be grateful to ASN for giving me the opportunity to present a poster at Kidney Week 2016. This one presentation provided a jump start to my career.

In my research study, I quantified soda acidity/phosphorus levels and conducted a soda-consumption survey. As is known, the potential health implications associated with soda overconsumption include heart/bone disease and calciphylaxis. During Kidney Week, I attended an oral presentation by Mona Calvo, PhD, a retired official from the US Food and Drug Administration (FDA), who offered me the opportunity to conduct research at the FDA. In July 2017, I spent two weeks interning at the FDA in Washington, DC, under the mentorship of Beverly Wolpert, PhD, the FDA epidemiology branch chief, and then continued the research by telework from Columbus, Georgia. Throughout my senior year of high school, I continued my research with the FDA correlating beverage consumption to education, income, race/ethnicity, and age in 14- to 18-year-old participants in the 2009 to 2014 National Health and Nutrition Examination Survey. In July 2018, I presented my research to the entire epidemiology branch team. My research abstract, of which I was first author, was published in the 2018 *JASN*. I thank Dr. Calvo, Dr. Wolpert, and the FDA epidemiology branch team for supporting my research pursuits.

After my FDA epidemiology study, I began a new study that aimed to correlate uric acid level (hyperuricemia and gout) to cardiovascular disease (CVD), hypertension, and chronic kidney disease stage. This study abstract, of which I was first author, was published in both the 2019 *JASN* and the 2020 *American Journal of Kidney Diseases* and was accepted for a poster presentation at the 2020 National Kidney Foundation (NKF) spring clinical meetings.

Now an Emory University undergraduate, I am performing research with Dr. George Beck Jr., PhD, at the Emory School of Medicine, working toward publishing my work on dietary phosphorus intake, mice kidney/liver tissue, and gene expression.

Tell us about your personal and educational advancements since our 2016 interview.

I am currently a biology major on the premedical track and a Robert W. Woodruff scholar at Emory University.

Each month, the Woodruff scholars program holds networking events to help foster students' connections with accomplished professionals across all disciplines—whether medicine, law, arts, or humanities. The program also provides scholars with travel grants to attend research conferences and summer internships, and it offers study-abroad programs.

Students may begin to view nephrology in another light if they are provided foundational support from the nephrology community from an early age.

Besides its strong academics and world-class research facilities, Emory also has an outstanding liberal arts program that allows me to take courses outside of my major—music, sociology, psychology—and actively participate in musical groups on campus. I sing in the Emory Concert Choir and serve as musical director of Emory Suri Bollywood Fusion A Cappella.

Congratulations on having another poster presented at the 2020 NKF spring clinical meetings. Tell us more about it.

I was ecstatic when I received the news that my poster was accepted for presentation because I was eager to share the study's important findings. Elevated uric acid (hyperuricemia) is a common finding in both general practice (internal medicine, family practice) and nephrology practice patients. Recent studies have revealed associations between hyperuricemia and diabetic retinopathy, hypertension, and other comorbid conditions; however, the data is still insufficient to confirm these findings. In hopes of providing stronger evidence to help physicians decide whether or not to treat hyperuricemia, I conducted a research study with my father, Raj Alappan, MD, that aimed to correlate uric acid level to CVD, hypertension, CKD stage, and demographics in patients with hyperuricemia and gout.

Data analysis revealed that patients with hyperuricemia and gout experienced significantly higher CVD occurrence ($p < 0.00001$) than did patients from a previous study (all practice patients from 2014 to 2016; work presented by my older brother, Harish R. Alappan, during ASN Kidney Week 2017). Overall, in hyperuricemic, gout, and CVD disease populations, uric acid level and CKD stage showed a strong, positive, linear correlation. White individuals with CVD had higher uric acid than did black individuals with CVD ($p = 0.03$). Young men (<65) had significantly lower CVD occurrence (23.48%) than did older men ($p = 0.031$); yet CVD occurrence did not statistically differ between younger and older women.

I hoped that presenting these findings at NKF would encourage physicians to consider preemptive treatment of all hyperuricemic patients—or at minimum, gout patients with uric acid ≥10 mg/dL—to mitigate the potential development of gout, CVD, and hypertension. When I first received news that the 2020 NKF spring clinical meetings would be moved to a virtual format because of the COVID-19 outbreak, I was disappointed. I believed I would not be able to share my findings as efficiently.

Nevertheless, the NKF did a great job ensuring the success of the online format. Lectures and oral presentations were held using the Zoom online platform, allowing me to attend sessions and learn from medical professionals and nephrologists just as I had done at ASN Kidney Week. Soon after uploading my poster to the NKF 2020 abstracts and e-poster gallery, I was contacted by several organizations that hoped to feature my poster and research, including *MedPage Today* and *Renal & Urology News*. I was excited to share my findings with a large audience of physicians.

What do you hope to accomplish next?

Following in the footsteps of my brother Harish, I hope to continue research with my current mentor and publish a research paper before I graduate from Emory. Harish performs research with the Emory School of Medicine

nephrology department under the mentorship of Charles O'Neill, MD. He has presented four different research posters at ASN meetings (2017, 2018, and 2019). Like Harish, whose article "Warfarin Accelerates Medial Arterial Calcification in Humans" was published in the April 2020 *Arteriosclerosis, Thrombosis, and Vascular Biology*, I hope that after graduating from Emory and before entering medical school I will have advanced my research and medical career by publishing a research paper.

I also hope to have further developed my musical abilities by traveling and competing with the Emory Concert Choir and Emory Suri A Cappella.

But my main priority now is to support those in need during the COVID-19 pandemic. After Emory announced that the remainder of the spring 2020 semester would be held online, I returned to my hometown, Columbus, GA. My parents, Drs. Raj and Devica Alappan, have worked very hard to see patients and coordinate with our local city leadership to determine what our family can do to help. After our local MercyMed nonprofit organization in Columbus created a COVID-19 testing clinic, we offered to analyze the data of over 1200 patients to determine potential comorbidities, symptoms, and other factors associated with the virus. I have been working remotely with the Emory/Atlanta MedSupplyDrive to help redirect unused personal protective equipment from idle research laboratories, institutions, and local businesses to hospitals, emergency rooms, and clinics. Because clinicians are running out of personal protective equipment, they are putting themselves at high risk through their contact with and treatment of COVID-19 patients. This puts their own lives and their patients' lives on the line.

In our last interview, I asked where you saw yourself in 10 years. Now, where do you see yourself in another 10 years? Is there a particular aspect of nephrology that interests you?

In my previous *ASN Kidney News* interview, I stated that in 10 years I hoped to have "attended a prestigious undergraduate university [and] well-respected medical school…conducted advanced research…settled down with a husband to start a family [and] served as an inspiration to students." Hopefully, in another 10 years I will be 1 year away from becoming a kidney specialist, will have published several research papers, and will be settled down with a family. I also hope to still have time for my hobbies: voice, piano, dance, and golf. Although my aspirations have not changed since my initial *ASN Kidney News* interview, I believe my experiences over the past 4 years have helped me to more clearly define my goals and rationale for pursuing a medical career in nephrology.

During the time since our last interview, I have become heavily involved in mentoring programs in hopes of sharing my research/science knowledge and serving as an inspiration to students. As a senior in high school, I visited Lonnie Jackson Academy, a local inner-city elementary school, to give a lecture on the importance of proper nutrition as it relates to soda acidity/phosphorus levels, beverage consumption, and hidden food/beverage phosphorus preservatives. My goal was not only to educate and promote proper nutrition in the younger generation but also to spark an interest in science and research. A few months later, my brother and I created an official ASN podcast to share our experiences as the "youngest Kidney Week presenters" in order to encourage other young scientists to pursue a career in medicine and nephrology. Now at Emory, I help teach chemistry and hold learning/mentoring sessions. I also serve as an undergraduate research programs research ambassador, helping students become involved in undergraduate research and assisting them in creating abstracts, drafting research proposals, presenting posters, and more.

Since 2015 I have served as a volunteer for Piedmont Columbus Regional Hospital in my hometown. In 2019, I shadowed several physicians and surgeons and observed more than 11 surgeries. This firsthand experience in the medical/surgical environment was pivotal in solidifying my interest in pursuing medicine. At the time, I was in the process of completing the uric acid study that was accepted as a poster presentation for the 2020 NKF spring clinical meetings. Before this study, my previous nephrology-related research concerned dietary phosphorus as it relates to nutrition, beverage and phosphorus consumption, hidden phosphorus in food/beverage preservatives, and potential adverse health implications (calciphylaxis, heart/bone disease). I had hoped to diversify my nephrology interests by performing a study centered on new topics, such as uric acid and gout. But I somehow drifted back to the topic of phosphorus and kidneys after the conclusion of the uric acid study. Now in the laboratory of Dr. George Beck at the Emory University School of Medicine, I perform research concerning dietary phosphorus intake, mice kidney/liver tissue, and gene expression. After 4 years, I have determined that I am passionate about nephrology, especially in relation to dietary phosphorus.

As you know, the nephrology workforce is shrinking. Not many people are interested in going into nephrology today. As someone who is very young in your career, yet with a lot of motivation and a strong interest in the field of nephrology, what would be your advice to your peers? To leaders in nephrology?

The best advice I can give is to seize every opportunity and resource as it comes, especially early in life. At age 16, I was exposed to many opportunities that were crucial in my career development, including the FDA internship and opportunity to present my poster during ASN Kidney Week 2016. My experience at Kidney Week also led me to other medical professionals who have provided me with considerable support, resources, and opportunities, including Matthew Sparks, MD, assistant professor of medicine at Duke University, and Edgar Lerma, MD, FASN, of the *ASN Kidney News* editorial board. Most important, it gave me the confidence and support to continue to pursue nephrology-related research and a career as a kidney specialist.

Since 2016, I have been in contact with many current and past ASN presidents and ASN Council members about ways to foster a similar interest in nephrology in other young scientists. For example, ASN could create a high school/undergraduate research forum for students to present their research at ASN meetings, where they could also meet other medical professionals and nephrologists and receive constructive feedback. Students could submit a research abstract or brief study description by way of application for the forum, and those selected would be invited to present their poster or oral presentation at the meeting. Alternatively, ASN could create a virtual forum by Zoom or Skype.

Another idea is to create an ASN Twitter or Facebook group chat for high school and undergraduate students to discuss nephrology-related topics, share personal research accomplishments, and network with the ASN community. Further, to inform high school and undergraduate students of new developments in nephrology, we could create a newsletter featuring nephrology research performed by students all over the world. The newsletter could showcase various nephrologists and medical professionals willing to allow students to meet or shadow them and provide information about upcoming nephrology research internships and summer research programs. Just at Emory alone, I know of several peers who would benefit from the opportunities these programs could provide.

Students may begin to view nephrology in a different light if they are provided foundational support from the nephrology community from an early age. Perhaps implementation of these ideas would provide just the impetus we need to boost interest in the field of nephrology.

Industry Spotlight

DaVita Invests in Wellth

DaVita (Denver, CO) has contributed an undisclosed amount to a round of funding for Wellth, a new company that uses behavioral economics principles to improve chronic-disease patient compliance with treatments in many areas of health. DaVita and Rock Health were the two new contributing members to the total of $10 million that Wellth, based in Los Angeles, raised recently. Top contributors include Boehringer Ingelheim Venture Fund and yabeo, a German investment firm that supports "young, innovative companies."

What do these companies like about Wellth, and what is its approach? The company has developed a platform that provides financial incentives and positive feedback when patients reach health compliance milestones. Wellth's products combine mobile technologies with behavioral economics concepts to help patients keep track of and adhere to their most important health activities over time. By delivering 89% care plan adherence, Wellth says its products can reduce complex patient costs by a range of $1500–$4500 per patient per year.

The Wellth website provides examples of the types of human behaviors and susceptibilities that can be used to gain better patient compliance. As an example of financial incentives, one study referenced on the website provided an up-front incentive payment if a person takes 7000 steps per day. Yet, better health outcomes were observed in the group docked $1.40 each time they failed to comply than in the group who earned $1.40 for each 7000-step compliance day completed. This tactic is based on loss aversion principles: people are more loath to lose money they have received than they are to accumulate money.

Loss aversion is just one of the techniques the company can employ to keep patients on track to better health. Other techniques include mobile phone technologies for photograph compliance check-ins, messages, and resources, along with deliberate human feedback.

Wellth is now partnering with DaVita around a shared ambition to serve the high-risk, high-need patient population from chronic kidney disease through transplantation, DaVita announced.

Dialysis patients often have an average of 11 daily medications, multiple dialysis sessions per week, and stringent nutritional guidelines, the dialysis provider noted.

"DaVita Venture Group's investment in Wellth continues our commitment to caring for the whole health of our kidney disease patients, who must navigate complex care plans," said Steve Phillips, vice president of DaVita Venture Group. "Wellth's platform has the potential to enable new models of patient engagement and drive further transformation for the 200,000 patients we serve." ■

Kidney Cancer Round-Up

The US Food and Drug Administration (FDA) has agreed once again to review a kidney cancer drug for approval, and noteworthy results from a phase 3 trial of a different drug for kidney cancer may yield further exploration.

Aveo Pharmaceuticals (Cambridge, MA) filed a New Drug Application (NDA) with the FDA. Aveo is seeking approval for tivozanib (brand name Fotivda), a vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI) to treat relapsed or refractory renal cell carcinoma (RCC). The drug was approved for the European market in 2017.

Aveo failed to obtain US approval in 2013 and again in the fall of 2019, when the FDA ruled that it remained concerned about the results of the TIVO-3 trial. In November 2019, Aveo noted that the FDA denied approval in part because "median OS (overall survival) for tivozanib is worse than that of sorafenib," a drug co-developed and co-marketed by Bayer and Onyx Pharmaceuticals as Nexavar, a treatment for primary kidney cancer (advanced RCC).

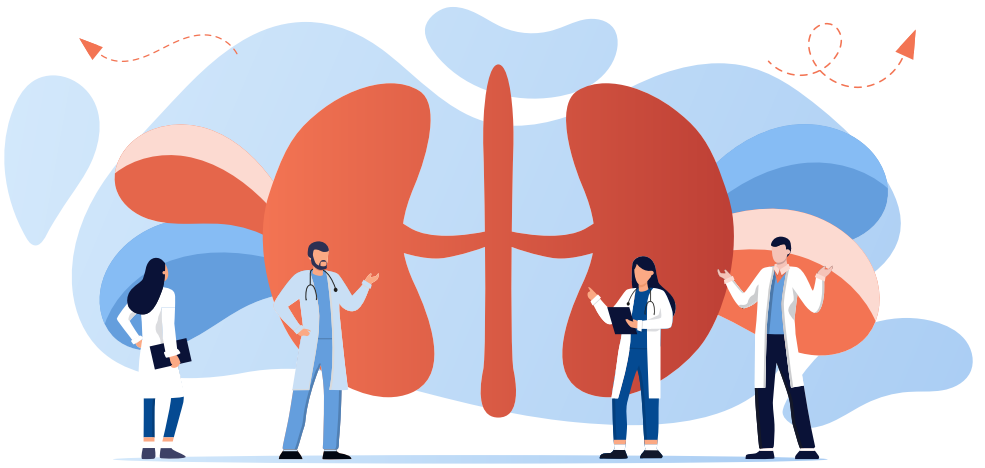
Aveo said in a presentation of results at the American Society of Clinical Oncology (ASCO) 2020 Virtual Scientific Program that tivozanib showed an increased median progression-free survival when compared with sorafenib. It is now in the FDA's court.

At the same meeting, researchers announced positive results for the drug savolitinib, a small-molecule MET tyrosine inhibitor aimed at treating patients with advanced papillary RCC (PRCC). Savolitinib is being developed by AstraZeneca and Chi-Med (based in Hong Kong).

Precision Oncology News reported that after promising phase 1 and 2 trials, a research team headed by Director Toni Choueiri of the Dana Farber kidney cancer center explored whether the drug might improve progression-free survival for locally advanced or metastatic PRCC cases involving MET drivers.

The phase 3 SAVOIR trial ended early, however, with just 60 patients enrolled (rather than the target number of 180) when researchers discovered that the comparator drug sunitinib (Sutent by Pfizer), approved for treating RCC, had released promising data. The data from Pfizer (based in New York, NY) showed that sunitinib had similar effects on the parameter of time-to-disease-recurrence in patient cases that did or did not involve MET drivers.

Because savolitinib showed promise, such as a non-statistically significant difference in median progression-free survival time of 7 months for savolitinib compared to 5.6 months in the sunitinib group, Choueiri said that further investigation of savolitinib is warranted. ■



Dapagliflozin Trial Stirs Controversy

A new trial with the sodium-glucose cotransporter 2 inhibitor (SGLT2i) dapagliflozin (brand name Farxiga) is recruiting COVID-19 patients with type 2 diabetes and other conditions to assess whether the drug can reduce COVID-19 progression.

However, the 900-patient, placebo-controlled DARE-19 trial (Dapagliflozin in Respiratory Failure in Patients with COVID-19) with the drug is proving controversial.

The AstraZeneca (Cambridge, UK) trial of dapagliflozin calls for COVID-19 patients with a history that includes at least one of these conditions: type 2 diabetes, hypertension, atherosclerotic cardiovascular disease, heart failure and/or chronic kidney disease stage 3 to 4 (eGFR ≥25 mL/min/1.73 m^2).

During the pandemic, many physicians are avoiding the use of dapagliflozin in diabetic patients with the new virus because of an increased risk of diabetic ketoacidosis. The trial aims to determine feasibility of the drug as a treatment option for COVID-19 patients at risk for developing complications like organ failure.

Recently, an international group of diabetes experts published an article in *The Lancet: Diabetes and Endocrinology* that recommended the following precaution: "Regarding medications, the panel advises that both metformin and sodium-glucose cotransporter 2 inhibitors be stopped in patients with COVID-19 and type 2 diabetes to reduce the risk of acute metabolic decompensation." Likewise, Diabetes UK has issued this guidance: "If you have type 2 diabetes and you take SGLT2i tablets, you can keep taking these unless you become unwell. If you are unwell, these tablets could increase your risk of developing diabetic ketoacidosis."

Two other makers of SGLT2i drugs have commented on whether they plan trials with their drugs, the *New York Times* reported. Johnson & Johnson (New Brunswick, NJ) has no plans for a COVID-19 trial with its drug, Invokana (canagliflozin), which slows the progression of kidney failure, the paper reported.

Boehringer Ingelheim and Eli Lilly (Ingelheim am Rein, Germany, and Indianapolis, IN), makers of Jardiance (empagliflozin), which helps improve blood sugar control and cardiovascular risk in type 2 diabetes, stated that they are "carefully assessing" products as potential COVID-19 treatments. The companies note, however, that Jardiance users who have acute illness have a greater ketoacidosis risk.

In answer to those challenging the trial, AstraZeneca has stressed that type 1 diabetic patients with COVID-19 will not be enrolled in the trial and that participating patients will be closely monitored for safety by an independent data monitoring committee. Results of the trial are expected in December 2020. ■

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

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Please Circle Degree:

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ASN American Society of Nephrology

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Metabolic Acidosis
Insights®

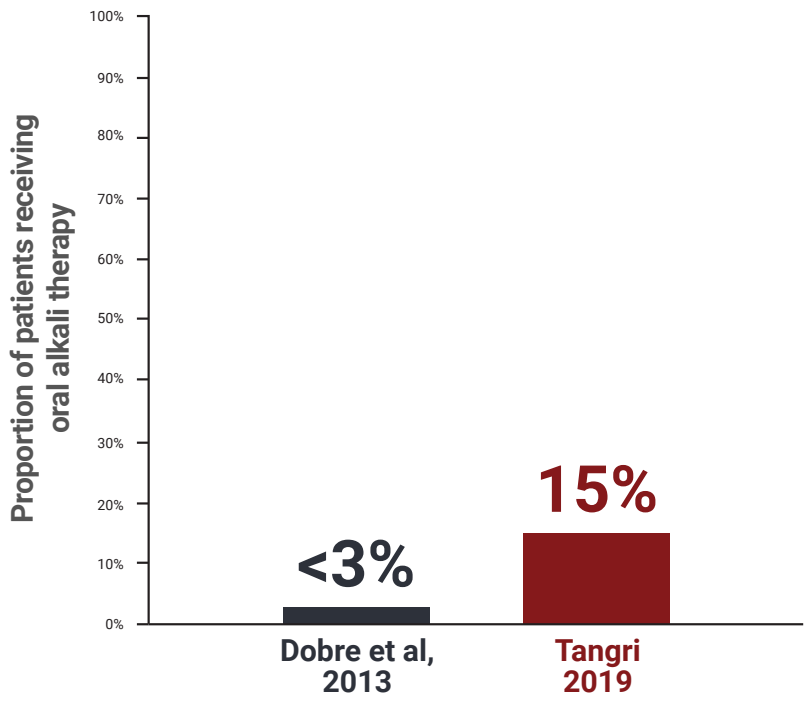
CHRONIC METABOLIC ACIDOSIS IS **UNDERTREATED**[1,2]

A growing body of evidence shows that metabolic acidosis is undertreated in patients with chronic kidney disease (CKD)[1,2]

- An analysis of claims and prescription data from a cohort of over 80,000 patients with laboratory data indicative of unequivocal Stage 3-5 CKD and chronic metabolic acidosis showed:
  - Metabolic acidosis was treated in 15.3% of the cohort[1]

- In the Chronic Renal Insufficiency Cohort (CRIC) study, a longitudinal study of over 1000 patients with Stage 2-4 CKD and metabolic acidosis:
  - Less than 3% of the cohort were treated with oral alkali therapy[2]

PATIENTS TREATED FOR METABOLIC ACIDOSIS[1,2]



Learn more at **MetabolicAcidosisInsights.com**

References: 1. Tangri N. Metabolic acidosis is underdiagnosed and undertreated in patients with chronic kidney disease. Poster presented at: American Society of Nephrology Kidney Week 2019; November 5-10, 2019; Washington, DC. **2.** Dobre M, Yang W, Chen J, et al. Association of serum bicarbonate with risk of renal and cardiovascular outcomes in CKD: a report from the Chronic Renal Insufficiency Cohort (CRIC) study. *Am J Kidney Dis*. 2013;62(4):670-678.

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