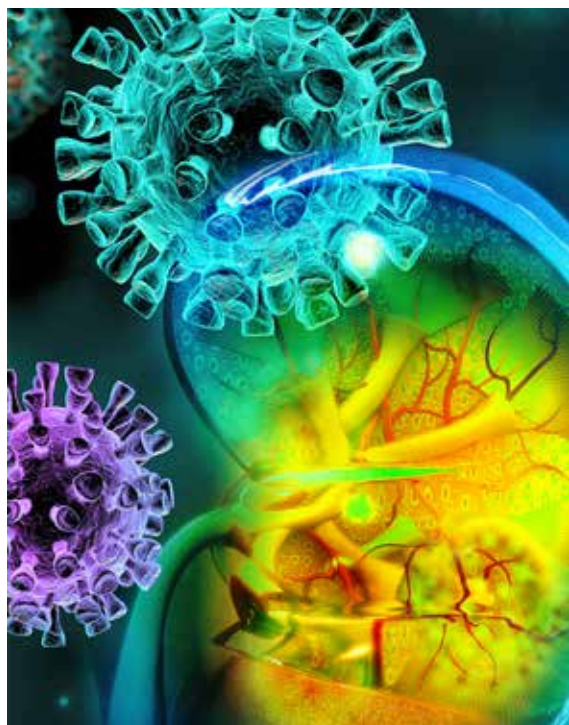


# KidneyNews

June 2020 | Vol. 12, Number 6

## COVID-19 Likely Launches Multipronged Attack on Kidneys

By Bridget M. Kuehn



**T**hree-quarters of patients hospitalized with COVID-19 pneumonia developed blood or protein in their urine or acute kidney injury, according to a study at a Chinese hospital. Nearly 1 in 10 of these patients died compared to about 1 in 100 patients without kidney injury (1). Other studies have reported 25% to 27.8% rates of acute kidney injury in patients with severe COVID-19 (2).

These alarming data have created a sense of urgency to efforts to understand the mechanisms that contribute to kidney injury in patients with COVID-19 and to find ways to protect the kidneys and improve patients' chances of survival.

Although most people who become infected with SARS-CoV-2 virus develop mild or no symptoms, a small subset become severely ill and require hospitalization and intensive care, explained Claudio Ronco, MD, director of the Department of Nephrology Dialysis & Transplantation at the International Renal Research Institute in Vicenza, Italy. Both the very serious illness these patients experience and the life-saving care they receive can have detrimental effects on the kidney. Additionally, there is

emerging evidence from autopsies of patients who died of the disease that SARS-CoV-2 can directly infect kidney cells.

"The fundamental question here is whether the acute kidney injury seen in COVID-19 is it just part of a more generalized picture of multiorgan failure, where other systems are failing and the kidneys are also failing, or whether the SARS-CoV-2 virus has a direct effect that's able to cause kidney injury," said Raghu Durvasula, MD, MHA, associate chief medical officer and medical director of hospital services at Northwest Kidney Centers in Seattle.

### A perfect storm

Critically ill patients often experience acute kidney injury even without the added burden of COVID-19, Durvasula said. So, it is not surprising that critically ill COVID-19 patients also often develop kidney injury.

"The kidneys are often just an innocent bystander when things are bad elsewhere in the body," he said.

Patients with severe COVID-19 often develop pneumonia that may progress to the life-threatening condition

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## Rural Health Hit Hard by COVID-19 Shutdown

By Melanie Padgett Powers

**S**ault Ste. Marie, Michigan, had only two confirmed COVID-19 cases by early May, but the pandemic was still hitting its healthcare system hard. With the small city's War Memorial Hospital mostly shut down and elective procedures postponed, the hospital was on shaky financial ground.

"My biggest concern is how all of this will impact the overall financial viability of our hospital," said David Jahn, War Memorial president and CEO. In early May, the hospital was projecting revenues would be down for the year by

40%, or \$35 million, if the coronavirus shutdown continued. The loss is not sustainable, Jahn said.

Eighty percent of the hospital's revenue is from outpatient services, which declined by 53% in April. That tracks with the national average—79% of rural hospital revenue is from outpatient care, according to the Chartis Center for Rural Health. The center is part of the Chartis Group, a healthcare advisory and analytics services firm.

As states shut down across the country, elective proce-

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Get up to date on recent cardiovascular interventions and their impact in patients with kidney diseases



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Better long-term outcomes from early AKI resolution



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Balancing education with safety requires new modes of interaction among trainees, patients, and educators





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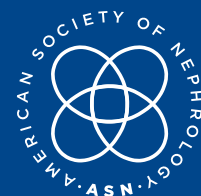
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## Rural Health Hit Hard

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dures and surgeries stopped. And while War Memorial's emergency room was open, "people are just not coming in at this time—maybe because they are afraid or maybe they are delaying much-needed care, which will exacerbate itself in the coming weeks and months," Jahn said.

Rural hospitals are essential for people with kidney diseases. While small hospitals do not often do transplants, they provide a nearby lifeline for transplant and dialysis patients experiencing complications or needing routine follow-up care. In addition, some hospitals provide outpatient dialysis.

War Memorial Hospital's outpatient dialysis center remained open this spring, implementing physical distancing rules and requiring everyone to wear masks. If finances forced the hospital to close permanently, it would be disastrous for the facility's 47 dialysis patients, said nephrologist Mohammed Haider, MD, director of the dialysis center. "You cannot close this unit, whatever happens to the hospital," he said. "The community has to run this center; otherwise, people will die."

Sault Ste. Marie sits on Michigan's Upper Peninsula, nearly 350 miles from Detroit. If the hospital closed, patients would have to travel much farther for care. The next nearest dialysis center is about a three-hour roundtrip, according to Haider. "This is a rural place. Driving three times a week will be very difficult," he said. "It's not sustainable."

Haider said he worries that patients would stop going to dialysis regularly because of the distance. Older, sicker, and/or poorer patients often rely on other people to drive them to appointments, he explained. "Dialysis not only affects the patient," he said. "It affects the whole family. It becomes a big burden on the family, too."

### Struggling hospitals

There are 2200 rural hospitals in the US. A little over half of them are critical access hospitals, a federal designation that requires hospitals to maintain a certain number of inpatient beds. That can be a challenge. Various federal programs over the years have buoyed the system to keep these hospitals open, but federal support continues to shrink, said Michael Topchik, MA, director of the Chartis Center for Rural Health.

These hospitals have little to no operating margin. One small hit—or one giant hit like a pandemic—can shut them down. Five years ago, 1 in 3 rural hospitals were operating at a loss. In 2020—before the pandemic—nearly half were.

In the past decade, more than 120 rural hospitals closed, Topchik said. Twenty of those closed within the past year. Chartis research from February 2020 named 453 rural hospitals vulnerable to closure.

"Rural hospitals disproportionately rely on outpatient procedures," Topchik said. "The government has mandated a shutdown of virtually 80% of a hospital's business, so these rural hospitals are suddenly out of the frying pan and into the fire."

Chartis research showed that the average "days of cash on hand" for rural hospitals is 30 days. Some hospitals only have 10 or 20 days of cash on hand, Topchik said. "The vulnerability of rural hospitals cannot be overstated, and the outpatient dimension is essential. It's really essential to what they do."

Although it is not yet apparent how many rural hospitals will close because of the coronavirus shutdown, the pandemic will be "the final nail in the coffin" for hospitals barely hanging on, Topchik predicted. In March 2020, a physician group's planned purchase of Haskell County Community Hospital in Stigler, Oklahoma, was halted because of the pandemic. The hospital medical staff was down to eight nurses.

### Decline of rural healthcare

Nephrologist Mohamed Sekkarie, MD, MPH, of Bluefield, West Virginia, has been a witness to the decline of rural healthcare since he arrived in coal mining country in 1990.

He now works in private practice with another nephrologist and a nurse practitioner and sees patients at Bluefield Regional Hospital. The hospital does not provide outpatient dialysis. Instead, three Fresenius freestanding clinics in the area cover about 200 dialysis patients, Sekkarie said.

In the 1990s, Bluefield's hospital was "almost tertiary care," he said, with 265 beds and multiple specialists. In 2010, the hospital was acquired by subsidiaries of Community Health Systems Inc. Last year, nearby Princeton Community Hospital Association bought Bluefield. In April 2020, Princeton closed Bluefield's ob-gyn and surgical services departments, affecting 68 employees.

Many healthcare specialists have also fled. The Bluefield area used to have three urologists, according to Sekkarie. Now there are none. "That is an essential specialty, especially when you talk about the geriatric population, Sekkarie said.

In May this year, inpatient dialysis was eliminated at Bluefield's hospital, he said. Inpatients who need dialysis must now be transferred to Princeton, West Virginia, 15 miles away. "It's a vicious cycle of fewer services and more patients going outside the area for care," he said.

**These hospitals have little to no operating margin. One small hit—or one giant hit like a pandemic—can shut them down.**

"I think things are falling apart in general.... Many people have left the area," Sekkarie said. "Gradually, the services provided at the hospital are going down because there is less need. And patients tend to be poorer with more disabilities."

Because of the pandemic, Princeton halted dialysis access surgery and interventions, unless it was an emergency complication. Instead, patients must make a four-hour round trip to Roanoke, Virginia, to a vascular access facility. "That is not unique to rural areas, but in big cities there are vascular access centers everywhere," Sekkarie said.

Even financially secure hospitals have taken a hit from the pandemic closures. Nephrologist Scott Bieber, DO, with Kootenai Clinics in Coeur d'Alene, Idaho, does rounds at Kootenai Health's 330-bed community-owned hospital, as well as two of its rural clinics. As of early May, the hospital had lost an estimated \$15 million in revenue, according to Bieber. Executives' paychecks were cut 10% beginning in March, and by May, providers' paychecks were also reduced by 10%.

"The whole thing just exposes how dependent hospitals are on elective procedures," Bieber said. "It really highlights a serious problem with how healthcare is paid for in this country, and it's not just our system that is struggling. Hospitals all over the country have been impacted."

One of the things Bieber worries about most is if the hospital begins cutting support staff, such as nurses and medical assistants, or rural outreach programs to help manage costs. "Those ancillary services and rural outreach programs are really the front line services that we need to take care of our patients," he said. But those programs are expensive and don't reimburse particularly well. "When things get lean, I am worried those will be the first to get cut."

Also essential are the smaller, even more rural hospitals, he said. While those facilities do not offer kidney care or dialysis, it's where residents can go for their lab tests and

imaging services, preventing them from traveling long distances. "These community hospitals make things a lot more convenient for my patients," Bieber said.

### Changes in kidney care

Like most aspects of society during the pandemic, there are a lot of unknowns in rural healthcare right now. Some hospitals started to open for elective procedures in May, but if a second wave of COVID-19 hits the country, everything might shut back down.

"Even as we start doing more elective cases, it's going to be slower than usual because of all the [COVID-19] screening procedures we have to do," Bieber said.

On the flip side, the pandemic has increased the implementation and use of telehealth. Telehealth is a concept that has existed for many years but has not always been widely available. Now it could be here to stay, increasing access to care for many patients. Video telehealth requires high-speed internet, which is not available in some rural areas. "Many of my patients live in rural mountain areas of Idaho that do not have reliable internet or cellphone service available," Bieber said. "We have been able to reach those folks with good old-fashioned telephone calls, and, thankfully, [the Centers for Medicare & Medicaid Services] has recognized that effort in recent payment changes."

A March survey by Sage Growth Partners showed that only 25% of the 500 respondents had used telehealth before the pandemic. Now, 59% said they were more likely to use telehealth, and 44% said telehealth services are available to them.

An ongoing pandemic and/or the closure of hospitals could also expand at-home dialysis. Patients with chronic kidney disease are a high-risk population, particularly vulnerable to COVID-19 complications. At-home dialysis would keep them away from dialysis clinics, reducing their potential exposure to the virus. And if a hospital dialysis clinic closed for good, home dialysis would be more convenient than half-day car rides three days a week.

"The option for home dialysis is something many rural patients choose because it minimizes the need for travel," said Jeffrey Hymes, MD, chief medical officer for Fresenius Kidney Care and senior vice president of clinical and scientific affairs for Fresenius Medical Care North America.

"We have already seen record growth in home dialysis over the past year, which is increasing at nine times the rate of in-center treatments," Hymes said. "As we expand telehealth and connected health options, we hope that more patients, including those in rural areas, will feel confident with choosing home dialysis in the future."

### Financial relief

The federal government has furnished some financial relief to hospitals, but more is needed, Topchik said. In May, the Trump administration announced rural hospitals will receive a \$10 billion coronavirus package. Rural hospitals will receive no less than \$1 million each.

There is broad bipartisan support in Congress to help rural hospitals survive, he added. Two pieces of legislation in recent years that could get more traction include the Senate's Rural Emergency Acute Care Hospital Act, which would create a new Medicare classification to strengthen support for hospitals that have emergency rooms and outpatient services. But these hospitals would no longer be required to provide inpatient care.

The other bill, in the House, is the Save Rural Hospitals Act, which would eliminate the multitude of federal reimbursement cuts that have hurt rural hospitals. These include Medicare sequestration cuts and "bad debt" reimbursement cuts. Since 2013, Medicare "bad debt" is only reimbursed at 65%, requiring providers to absorb the other 35%.

"There's a recognition that something needs to be done," Topchik said. "It is a grave, grave crisis, and America is going to have to come to terms with it. I believe it's going to come down to ... a moral issue. We're going to have to decide as a society if we're going to make sure we provide healthcare to the roughly 60 million Americans who call rural America home." ■

## COVID-19

Continued from page 1

acute respiratory distress syndrome, which itself can damage the kidney, Ronco noted. High airway pressure from mechanical ventilation these patients receive to help them breathe may also inadvertently cause harm. The infection can set off a cytokine storm, a severe immune reaction in which the immune system floods the body with inflammatory chemicals that can also directly damage the kidney, he said.

“This is clearly a multifactorial situation,” Ronco said. “In these patients, there are several mechanisms that may induce damage to the kidney. Some of them are direct and some of them are indirect.”

Complicating matters, patients with COVID-19 often show up at the hospital dehydrated as a result of not feeling well, diarrhea, and not eating or drinking as much as they usually do, Durvasula said. And patients who need mechanical ventilation may be given diuretics to get rid of excess fluid in order to improve their oxygenation, which may inadvertently cause low fluid levels in the body, which, in turn, can contribute to tubular injuries or dysfunction, he said.

There is also emerging evidence that COVID-19 patients may be prone to developing blood clots. For example, Durvasula said he and his colleagues have seen COVID-19 patients receiving dialysis develop clots that block off their dialysis circuits requiring treatment with anticoagulating drugs.

“We are hearing reports that patients may similarly be developing spontaneous clots in large veins in their bodies,” he said. “This begs the question whether they may be forming clots in the small vessels of the kidney and that could be a mechanism of kidney injury.”

Ronco noted that the flood of inflammatory molecules caused by a cytokine storm can cause dysfunction in the lining of the blood vessels throughout the body and in the muscle tissue of the heart, and it can contribute to excessive clot formation. The kidney may also be directly damaged as it filters out harmful molecules (damage-associated molecular patterns) released by cells killed by the infection or inflammation. The immune system’s attempts to correct the excessive inflammation can also cause harm, he noted.

Currently, physicians are still relying primarily on supportive intensive care to help severely ill COVID-19 patients recover, Durvasula said. This includes trying to maintain an optimal amount of fluid in the body—not too much or too little. Ronco noted that maintaining optimal blood pressure and treating patients who develop clots with anticoagulant drugs can also help in the recovery of COVID-19 patients. Some anti-inflammatory drugs are also being used. Ronco and his colleagues are trying extracorporeal therapies that pump the blood out of the body to screen out some of the inflammatory molecules to help modulate the patient’s immune response (3). Although he cautioned there are not yet data from randomized clinical

trials to prove this is effective, “we only have expert opinion and experience.”

“It is an option for patients to gain time and have their immune system respond and possibly get better,” he said.

Several studies are underway of antiviral drugs to treat patients with COVID-19. The US Food and Drug Administration recently granted an emergency use authorization for the investigational antiviral drug remdesivir for severely ill COVID-19 patients (4). Preliminary results showed an 11-day average recovery time in patients taking the drug compared with a 15-day recovery time for those not taking the drug (5).

### Direct assault?

There is also emerging evidence that the virus itself may directly infect the kidney. Using histological techniques and electron microscopy, researchers from Wuhan, China, examined kidney samples from 26 patients who died of COVID-19 and showed the SARS-CoV-2 virus was present in the kidneys (6).

“It’s excellent work under some challenging circumstances,” said Evan Farkash, MD, PhD, who recently published results of an autopsy of a single patient from Michigan who died as a result of COVID-19 complications that confirms the presence of the virus in the kidney in renal tubular cells using similar techniques (7). Using light microscopy, he found that tubular cells infected with SARS-CoV-2 were filled with vacuoles. Farkash noted that a previous coronavirus that caused a global outbreak of severe acute respiratory syndrome in 2003 reproduces in vacuoles. This could be evidence that SARS-CoV-2 is replicating in the kidney cells, but more studies are needed to confirm this, he said.

Since then, Farkash and his colleagues have examined kidney tissue from more patients who died from COVID-19 and found that the virus is often present and can also be found in the glomerulus.

The angiotensin-converting enzyme 2 (ACE-2) receptor that allows the virus to infect lung cells also infects kidney cells. “Mechanistically, it makes sense that the kidney could be infected,” Farkash said. “The ACE-2 receptor is expressed at very high levels in the renal tubular epithelium. It is also expressed in endothelial cells as well as the podocytes in the glomerulus.”

But more study is needed to determine how big of a role it plays, Farkash said. He noted that in the patient whose autopsy results were published, the virus was only present in a small part of the kidney, suggesting that other mechanisms may have played a larger role in the patient’s kidney injury.

“The direct infection could have been an incidental finding, or it may have mattered very little or not at all,” he said. He noted the virus was more widespread in the kidneys of other deceased patients. But it may just be a manifestation of the widespread disease in the patients’ bodies, he said.

Durvasula called the autopsy findings “compelling.” He

also noted there is evidence from China of blood or protein in the urine of patients with COVID-19.

“When we hear descriptions of protein and blood in the urine, that tells us there is actually an intrinsic injury within the kidneys,” he said. Both Farkash and Durvasula noted that biopsy studies from living patients with COVID-19–related kidney injuries might provide more definitive evidence of the virus’ role in kidney injury. But such biopsies are not likely to be collected unless it may help guide patient care, Durvasula said.

Although there has been a recent explosion in the numbers of studies about the effect of COVID-19 on the kidney, there are still many questions that need to be answered. For example, Durvasula noted that the number of COVID-19 patients requiring dialysis in the intensive care unit has varied in different parts of the country, with 20% to 40% of patients needing such care in some parts of the country (8). But only about 5% of COVID-19 patients at the hospitals Durvasula works with have required renal replacement therapy.

“As much as we’ve learned, there’s still a lot we don’t know about the mechanisms of acute kidney injury in COVID-19 patients,” Durvasula said. ■

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## Kidney biopsies for research: safety and feasibility

Additional kidney cores for research purposes can be successfully and safely obtained from 90% of diabetic patients undergoing clinically indicated kidney biopsy, according to a research letter in *CJASN*.

The authors report an interim analysis from the multicenter Transforming Research in Diabetic Nephropathy (TRIDENT) study, a longitudinal cohort study using direct analysis of kidney tissue to identify biomarkers and new therapeutic targets for diabetic kidney disease. The analysis included data on 176 patients enrolled in TRIDENT. All had clinical indications for kidney biopsy and consented to undergo collection of an additional biopsy core for the study.

Biopsy was performed in 160 patients, and a research biopsy core was successfully obtained from 144 patients. The

reasons for not obtaining an additional core were operator’s decision or needing all tissue for clinical purposes in 10 cases and bleeding/hematoma in six cases. The mean number of biopsy passes was 3.6. The indications for biopsy were excessive proteinuria in 65% of cases and rapid loss of kidney function in 24%.

Diabetic glomerulosclerosis was present in 82% of eligible research cores. Eleven patients (7%) experienced a total of 19 complications. Hematomas >5 cm occurred in seven patients, gross hematuria in three patients, and unplanned blood transfusion in three patients. Six patients had a prolonged hospital stay or readmission, but none required surgery or radiologic intervention.

Diabetic kidney disease is usually a clinical diagnosis, based on blood and urine test results rather than direct anal-

ysis of kidney tissue. There are limited data on the feasibility and safety of obtaining kidney biopsy cores for research purposes, as planned by the TRIDENT study.

This interim analysis shows a high rate of successful research core recovery in diabetic patients undergoing clinically indicated kidney biopsy, with low rates of adverse events. “These data will help to potentiate the safety of obtaining kidney tissue for research, ultimately improving care for patients with DKD,” the researchers write. They plan a full analysis of biopsy complications and risk factors once TRIDENT recruitment is completed [Hogan JJ, et al. The feasibility and safety of obtaining research kidney biopsy cores in patients with diabetes: An interim analysis of the TRIDENT study. *Clin J Am Soc Nephrol* doi: 10.2215/CJN.13061019]. ■



# Evidence Mounts that RAS-Blocking Medications Pose No Danger to COVID-19 Patients

By Eric Seaborg

Many professional societies staked out the early position that COVID-19 patients should continue their blood pressure medications in the absence of a clear reason to stop them. And the early evidence to date has reinforced those recommendations.

It will take at least several months for more definitive answers from clinical trials, but the three largest observational studies to date found no signals of harm among patients taking inhibitors of the renin-angiotensin system (RAS) pathway.

Published in the May 1, 2020, *New England Journal of Medicine*, the studies are “definitely the biggest and most authoritative” so far, said Matthew Sparks, MD, assistant professor of medicine at Duke University. “The good news is, they do not show a signal for harm. The bad news is, it is retrospective data. This is a very challenging answer to get at with retrospective data. The only way we are going to know is with clinical trials, which are currently ongoing.”

The controversy was sparked by letters that appeared in *BMJ* and *The Lancet* in mid-March that raised a theoretical threat that angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) could increase the likelihood of COVID-19 infections and worsen their severity by encouraging a potential pathway for the SARS-CoV-2 virus to enter lung cells.

The letters received a great deal of attention in the general press as well as from medical professionals, according to Jordana Cohen, MD, assistant professor in the division of renal-electrolyte and hypertension at the Perelman School of Medicine at the University of Pennsylvania.

The letters noted two related areas of concern. First, they noted a possible link between severe COVID-19 infections and ACE inhibitors or ARBs based on studies showing that people who might be taking the drugs (on the basis of their pre-existing conditions) were in the groups experiencing more severe infections.

Second, they posited an explanation of why the drugs could worsen infections. Analysis of the molecular structure of the SARS-CoV-2 virus revealed a spike protein on its surface that can attach to receptors on angiotensin-converting enzyme 2 (ACE2) to gain entry into cells. Because some animal studies have shown that ACE inhibitors and ARBs may increase the expression of ACE2, and because ACE2 is expressed in the epithelial cells of the lungs, intestines, kidney, and blood vessels, patients taking the drugs could theoretically experience more severe infections.

The two letters “got so much press that patients were calling us and asking what to do,” Cohen said. “Some universities and practices actually released statements saying that you should be holding these medicines in anybody right now because of this theoretical risk, and that was with no data at the time.”

“This has been an active debate and an example of how little bits and pieces of basic science can lead you down paths that can really get you twisted around,” said Stephen C. Textor, MD, professor of medicine with specialties in nephrology and hypertension at the Mayo Clinic in Rochester, Minn. Many experts were concerned that patients might stop taking their medications on their own, just in case they became infected.

Professional societies quickly pushed back with statements and recommendations saying that there was no

evidence to support the withholding of these medications, so they should be continued in the absence of indications for stopping them.

By the end of March, the Nephrology Journal Club website, NephJC, had collected 14 such recommendations.

“After examining the available evidence, we advise that inhibitors of the renin-angiotensin system (RAS) pathway should be continued in patients with COVID-19 who are taking these drugs for evidence-based indications,” a group led by Sparks, who is co-curator of the NephJC COVID page, wrote in *CJASN* in early April. That article pointed out that although some studies have shown that the drugs increase ACE2 levels, others do not, so there is no evidence to conclude that RAS inhibitors are linked to upregulation of ACE2. (They set up a website with the latest COVID-19 information related to nephrology at [www.nephjc.com/covid19](http://www.nephjc.com/covid19).)

## Observational studies

Cohen said that the first retrospective studies on the use of the medications in COVID-19 patients added to the confusion by showing opposing effects—some found the medications were beneficial, some found them to be harmful, and some found neither.

But the weight of evidence shifted with publication of the large *New England Journal of Medicine* studies, and “none of the three studies showed evidence of harm with continued use of ACE inhibitors and ARBs,” according to an editorial accompanying the studies.

One was a database study of 8910 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.

A case-control study in the Lombardy region of Italy compared 6272 patients with confirmed COVID-19 with 30,759 controls matched according to age, sex, and municipality of residence. The study found no association between ACE inhibitors or ARBs with the likelihood of SARS-CoV-2 infection nor any association between the drugs and severe COVID-19 disease.

A study of more than 12,500 electronic health records of patients in the New York University health system found no positive association for ACE inhibitors or ARBs with either a COVID-19 infection or severe illness.

“Professional scientific societies and experts have spoken with one voice in advising that patients should not discontinue ACE inhibitor or ARB therapy out of a concern that they are at increased risk for infection, severe illness, or death during the COVID-19 pandemic,” the editorialists write, and “these three studies support those recommendations.”

But “the only way we are going to know the answer is with clinical trials because there are too many confounders in the decision to start and stop these drugs,” Sparks said. “The good news is, when the retrospective studies tried to match patients with propensity scoring, they have not found a signal for harm.”

Among the questions that observational studies can’t answer is an obvious one: Are patients with conditions like hypertension, diabetes, and cardiovascular disease experiencing more severe COVID-19 because of these underlying conditions or because of the drugs they are taking to treat the conditions?

## Beneficial effects?

And there is also that question of the drugs raising ACE2 levels—if that happened, would the effects necessarily be bad?

A *JAMA Cardiology* paper noted that in addition to its role as a pathway for the virus to enter cells, ACE2 “plays a major anti-inflammatory role in RAS signaling by converting angiotensin II, the quintessential perpetrator of inflammation, to angiotensin 1-7, which carries anti-inflammatory properties.” The authors note that ACE2 production declines with age such that “older individuals, especially those with hypertension and diabetes, have reduced ACE2 expression and upregulation of angiotensin II proinflammatory signaling.” They posit that lower levels of ACE2 could contribute to making COVID-19 worse, and that by restoring them to earlier levels, ACE inhibitors and ARBs could have a beneficial effect.

Cohen said that this paper illustrates that “there is so much that we don’t fully understand about factors that influence ACE2 expression and activity, and how that in turn may impact the development and severity of COVID-19. There are some studies that show that these medicines reduce inflammation in viral pneumonia and that they could potentially be helpful. There is some genuine theoretical risk and there are some genuine theoretical benefits.”

## Clinical trials

Sparks and Cohen both emphasized the need for randomized clinical trials to sort out the confounders and give more definitive answers. Cohen is a co-principal investigator of a multi-center, international trial that plans to enroll 152 patients hospitalized with COVID-19 who are already using an ACE inhibitor or ARB. The patients will be randomly assigned to either stop or continue taking the medication. The investigators will follow the patients to rank their outcomes based on their need for mechanical ventilation, need for renal replacement therapy, organ failure, and mortality. The trial began enrolling patients on March 31, 2020, and is expected to run for three or four months. It is “essentially unfunded,” with the healthcare providers and sites participating on a volunteer basis, Cohen said.

A large number of researchers must be stepping up in a similar fashion, because more than 1000 studies addressing various aspects of COVID-19 are registered at ClinicalTrials.gov, including more than 600 interventional studies and randomized clinical trials. At least a dozen of them are addressing the use of ACE inhibitors and ARBs.

Of course, clinicians must make decisions based on the evidence available now. Textor said that at the Mayo Clinic they “dug into the issue” and concluded that “it is a mistake to react to the theoretical issue when there has been no observed effect at all.”

Sparks summarizes the weight of evidence and guidance from expert opinion: “When you see a patient with COVID-19, you should do exactly what you would do with any infection in regard to their RAS blockade. If their blood pressure is fine, they have no hyperkalemia, and they have no other reason to stop their medication, then you continue it. If you do have a reason, then you stop it. COVID-19 should not figure into the equation on what to do.” ■



# Only one calcimimetic lowers and maintains key sHPT lab values with IV administration you control<sup>1</sup>

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

## Indication

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

## Limitations of Use:

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

## Important Safety Information

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

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

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

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

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

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

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

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

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

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

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

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

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

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



BRIEF SUMMARY OF PRESCRIBING INFORMATION



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<br>(N = 513) | PARSABIV<br>(N = 503) |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|-----------------------|
| Blood calcium decreased <sup>a</sup>                                                                                                                                                                        | 10%                  | 64%                   |
| Muscle spasms                                                                                                                                                                                               | 7%                   | 12%                   |
| Diarrhea                                                                                                                                                                                                    | 9%                   | 11%                   |
| Nausea                                                                                                                                                                                                      | 6%                   | 11%                   |
| Vomiting                                                                                                                                                                                                    | 5%                   | 9%                    |
| Headache                                                                                                                                                                                                    | 6%                   | 8%                    |
| Hypocalcemia <sup>b</sup>                                                                                                                                                                                   | 0.2%                 | 7%                    |
| Paresthesia <sup>c</sup>                                                                                                                                                                                    | 1%                   | 6%                    |
| *Included adverse reactions reported with at least 1% greater incidence in the PARSABIV group compared to the placebo group                                                                                 |                      |                       |
| <sup>a</sup> 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) |                      |                       |
| <sup>b</sup> Symptomatic reductions in corrected serum calcium < 8.3 mg/dL                                                                                                                                  |                      |                       |
| <sup>c</sup> 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 [<sup>14</sup>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 [<sup>14</sup>C]-etelcalcetide in lactating rats at maternal exposures similar to the exposure at the human clinical dose of 15 mg three times per week. [<sup>14</sup>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**<sup>®</sup>

PARSABIV<sup>™</sup> (etelcalcetide)

#### Manufactured for:

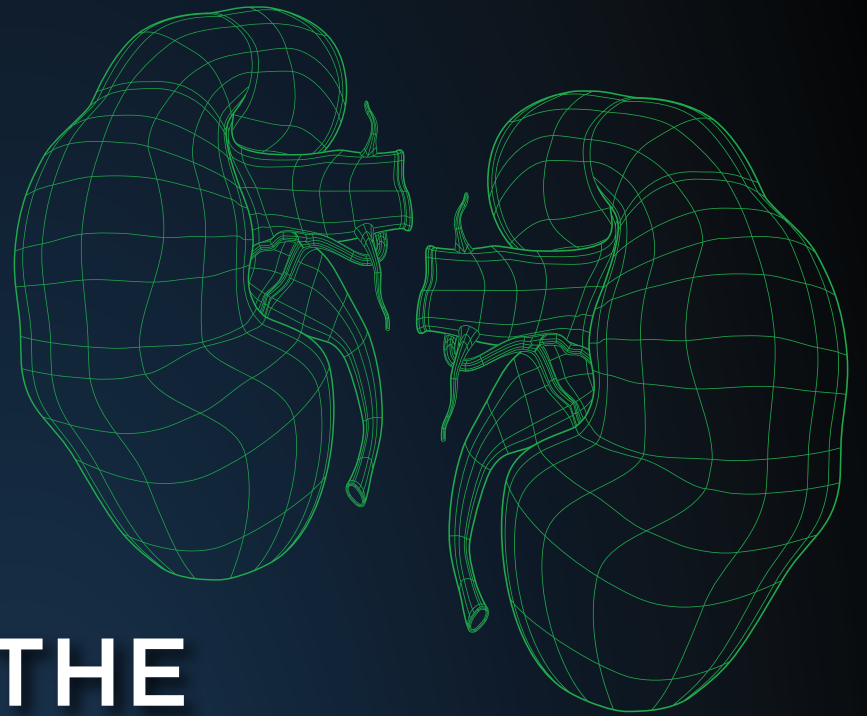
**KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc.**

One Amgen Center Drive  
Thousand Oaks, California 91320-1799

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

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# HELP ASN BUILD THE FUTURE OF KIDNEY CARE

Submit your innovative teaching tool idea to the  
ASN Innovations in Kidney Education Contest.  
**YOU COULD WIN A PRIZE WORTH \$5,000.**

## **What do virtual reality, simulation, and gaming have to do with nephrology?**

Well, everything if they are used as tools to inspire students and trainees to learn more about the field.

**Enter the ASN Innovations in Kidney Education Contest**, which aims to do just that. Participants develop creative tools to teach nephrology in new and exciting ways.

Previous winners have created a wide range of tools, some of which include a mobile-friendly learning website called NephSim; a virtual reality and gaming tool called Nephro360; a CRRT virtual patient simulator; renal pathology web episodes; and a board game focused on the physiology of the nephron.

Launched in 2015, the contest has spurred great interest about the field of nephrology and advanced new ideas for additional curricula development. It has also fostered meaningful interactions between medical and graduate students, residents, fellows, post-doc trainees, faculty, practicing nephrologists, researchers, and other health professionals.

**Full contest guidelines and eligibility requirements are available at [www.ASN-online.org/contest](http://www.ASN-online.org/contest).**



**Contest entries are due by June 12, 2020.**

*This contest is void outside the United States and where prohibited by law.*

# Nephrology Fellowship Education

## Moving Apart to Come Together during COVID-19

By Sam Kant and C. John Sperati



**S**ARS-CoV-2 infection, the causative agent of coronavirus disease 2019 (COVID-19), was declared a pandemic on March 11, 2020, with more than 1.4 million people afflicted by April 8, 2020, and more than 80,000 deaths (1). Physical distancing is the cornerstone of slowing disease transmission to mitigate an overwhelming demand for healthcare resources that exceeds capacity. This strategy was used as early as the fifth century BC (2), more recently during the 1918 influenza pandemic, and during the 2009 severe acute respiratory syndrome (SARS) and 2012 Middle East Respiratory Syndrome epidemics. Early physical distancing has in part been credited for the success Taiwan and Hong Kong have experienced in controlling SARS-CoV-2 transmission (3). Official recommendations for physical distancing in the United States began in March 2020.

Physical distancing, however, is the antithesis of medical education. Bedside teaching through rounding—originally championed by Sir William Osler at the Johns Hopkins Hospital—has been a cornerstone of medical education for more than 130 years. Those bedside interactions have grown over the years to include educational venues ranging in size from small group didactics to auditorium presentations. Preparations for and actual care of patients with COVID-19 have, literally overnight, required a transformation in how medical education is delivered to trainees. This certainly presents novel opportunities along with considerable concerns for the adequacy of ongoing instruction. Moreover, for specialties such as nephrology, which already face recruitment and training challenges, the loss of personal, small-group engagement may be yet another impediment to growing the specialty. The need to balance education with safety requires attention to workplace policies, formal didactics, and trainees' wellness.

### Workplace policies

Effective teaching requires receptive and engaged learners. Fellowship curricula can continue during a pandemic, but the workplace must first be structured to permit a learning environment. The safety of patients and providers is paramount, and well-delineated, informed clinical practice paradigms must be operational. Given the uncertainty and constant flux of information associated with

COVID-19, keeping abreast with current government, professional society, and local recommendations is a requirement for all training programs. Major resources for monitoring the pandemic and informing best practice include the Centers for Disease Control (<https://www.cdc.gov/coronavirus/2019-ncov/index.html>), the World Health Organization (<https://www.who.int/emergencies/diseases/novel-coronavirus-2019>), and the Johns Hopkins Coronavirus Resource Center (<https://coronavirus.jhu.edu/>). State and local health departments are of critical importance to local practice. Dialysis and transplant populations may be especially vulnerable during this period, and guidance is available from the American Society of Nephrology (<https://www.asn-online.org/ntds/>) and the American Society of Transplantation (<https://www.myast.org/covid-19-information>). NephJC (<http://www.nephjc.com/covid19>) has emerged as a focused, high-yield resource for nephrologists.

In addition, institutional dissemination of information should be structured to avoid overwhelming staff, trainees, and faculty. Information overload may cause significant stress and information fatigue syndrome (4). Summarized digests of information distributed several times a week or once a day are manageable. We have maintained a continuously updated, highly curated repository of information specific to operations, clinical care, and trainee education in a division-wide OneNote (Microsoft Corporation, Redmond, WA) notebook accessible by phone and desktop app. A weekly division-wide interactive videoconference (IVC) town hall meeting that includes all faculty, trainees, and staff allows for social connection, updates to major initiatives, and an opportunity for questions.

With respect to inpatient workflow, given that most nephrology programs operate multiple simultaneous consultation teams, consider assigning COVID-19–positive patients and persons under investigation for COVID-19 to a single team to minimize exposure to providers. To conserve personal protective equipment (PPE), these patients are usually evaluated at the bedside only by the attending nephrologist. Billing requirements have evolved quickly during this crisis, and it is now often possible for the provider to communicate with a patient through IVC without entering a protected zone.

Although the threat of infection should not prevent ap-

propriate medical care, there are times when the trainee and attending nephrologist can deliver effective nephrology care without always having to be at the bedside. This was likely not envisioned by Osler, and it is imperative that clinicians and educators do not succumb to this slippery slope. Technology can be leveraged to this end. Innovative approaches, such as the use of a head-mounted phone under PPE or camera-enabled workstations on wheels, can allow multiple team members to engage in bedside clinical care through IVC while only one provider is at the bedside. Care providers such as pharmacists and case managers, for example, could even join rounds from an off-site location to maximize physical distancing in the hospital.

### Backup protocols for fellows, training program directors unable to work

It is critical to have defined protocols for backup clinical coverage should a fellow be unable to work. Moreover, all training programs should identify faculty and staff responsible for assuming control of the operations and accreditation of the fellowship if the program director and/or coordinator should be incapacitated. This backup plan should include ensuring that these individuals have the necessary credentials for accessing key electronic systems, both nationally and locally.

Whereas the pandemic has appropriately focused considerable effort on inpatient operations, maintaining continuity of outpatient care is critical. The nationwide rollout of telemedicine by IVC has rapidly expanded. The Accreditation Council for Graduate Medical Education, having originally planned for a July 1, 2020, beginning, issued emergency authorization on March 18, 2020, allowing trainees to participate in telemedicine visits where “the supervising physician and/or patient is not physically present with the resident and the supervising physician is concurrently monitoring the patient care through appropriate telecommunication technology.”

Multiple IVC solutions allow for the attending nephrologist to monitor the entire patient care encounter or to join at the conclusion of the visit. The attending can discuss the plan of care with the trainee by telephone or IVC after pausing the patient's audio and video connection. If rooms and camera interfaces compliant with the Health Insurance Portability and Accountability Act (HIPAA) are available, the trainee and attending can maximize physical distancing by remaining in separate locations. Rescheduling patients can be cumbersome initially, and we have used the following strategies to aid triage:

- 1 In-person: acute medical needs requiring physical examination and/or visit are paired with an intervention (e.g., injection of erythropoiesis-stimulating agent); the necessity of the evaluation needs to outweigh the risk of acquiring infection.
- 2 Telemedicine: medical needs requiring evaluation without physical examination.
- 3 Reschedule: safe to wait at least 2 to 3 months, thereby facilitating rollout of telemedicine to patients with greater need.

Given the unique precepting and educational needs inherent to the outpatient clinical training of fellows, it remains to be determined how telemedicine will be best used in the long run. Unquestionably, this is a practice environment in which fellows must now be fluent at the conclusion of their training, and our response to this pandemic will likely uncover novel applications for the technology.



Fellowship didactics

Acutely, structured education may be deferred while response plans are implemented. In its place, trainees receive firsthand experience in public health epidemiology, medical triage, crisis response, resource conservation, and rapid operationalization of translational medicine. The extent to which a program is affected by COVID-19–infected patients will dictate the timeline for returning to a more typical curriculum. Ultimately, however, the formal educational mission must continue as soon as possible, and trainee engagement needs to be sustained. Moving didactics to an IVC has helped mitigate this issue.

Interactive video conferencing has been used for some time as an adjunct in medical education and in nephrology specifically (5, 6). Programs such as the Glomerular Disease Study and Trial Consortium (Glom-Con) (<https://glomcon.org>) have succeeded at delivering educational content to participants around the world in real time. In that scenario, the achievement lies in delivering interactive content on a topic for which no in-person contact is expected. The current challenge is to engage participants locally who would otherwise expect the social interaction inherent in a group activity. When an IVC ends, participants instantly separate without opportunity for informal discussion, personal connection, or reinforcement of delivered content. Table 1 describes some advantages and disadvantages of IVC-based education. IVC is not limited to prepared didactics, and it can be used for “chalk talks” through on-screen annotation, kidney biopsy review, and real-time education in urine microscopy. Our program facilitated the transition to IVC through the initial use of lighter topics that required participation, such as NephMadness (<https://ajkdblog.org/category/nephmadness/>) and board review. The following guidelines can help ensure a productive IVC with maximal impact:

- 1 Use the same link for standing conferences and distribute to participants’ calendars.
- 2 Disseminate conference links to internal medicine residents and other interested divisions and departments.
- 3 Invite hospital programs that have fewer resources to maintain both clinical and educational activities during a crisis response.
- 4 If internet bandwidth permits, ask participants to enable their video links, thereby making interactions as in-person and focused as possible.
- 5 Mute microphones of nonspeaking participants during formal presentations.
- 6 Encourage audience participation through polls and individual participant-directed questioning; open-ended questions to the entire group do not work well.
- 7 Follow up a presentation with an email summary of learning points or questions to stimulate further learning.
- 8 Verbally present all content for the benefit of participants connected by audio only.
- 9 Shorten sessions to maximize attention and to allow for technical constraints on time.
- 10 Notify participants if the presentation is being recorded, because the material may be available for later review. Unquestionably, if protected health information is to be discussed, the IVC software must be HIPAA compliant, and software security settings should be reviewed to prevent third-party hacking (“Zoom-bombing”).

Trainee wellness

The psychologic effects of physical distancing and quarantine have been well documented. Healthcare workers subject to quarantine are known to experience exhaustion, detachment, and depression (7–10). Low mood and irritability are the most prevalent symptoms (11), and trainee burnout rates could rise during this period. We have attempted to strengthen resiliency and mini-

Table 1. Advantages and disadvantages of interactive video conferencing for didactic lectures

| Advantages                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Disadvantages                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Accessible from any location</b></p> <p><b>Encourages participation by individuals who are otherwise unable to attend in person</b></p> <ul style="list-style-type: none"><li>• Program-related participants (e.g., faculty, off-site trainees)</li><li>• Presenters with adjoining schedule commitments or from another institution</li><li>• Trainees in other disciplines (e.g., residents in internal medicine or other fields)</li></ul> <p><b>Facilitates presentation by multiple speakers with separate slide sets</b></p> <p><b>Questions can be posed to all participants by chat</b></p> <p><b>Allows for real-time literature searching by participants with posting of information by chat feature</b></p> <p><b>Presentation and chat dialogue are easily recorded to create an education library</b></p> <p><b>Not dependent on conference room availability</b></p> | <p><b>Presentations can be less engaging</b></p> <p><b>Rapid audience participation is difficult</b></p> <ul style="list-style-type: none"><li>• Participants must unmute the microphone</li><li>• Participants may multitask during the presentation and not pay attention</li></ul> <p><b>Less opportunity for free-flowing discussion</b></p> <p><b>Technical limitations</b></p> <ul style="list-style-type: none"><li>• Internet bandwidth may lead to suboptimal connections</li><li>• Software and hardware failures/errors</li></ul> |

mize the risk of burnout by acknowledging the resolve, sacrifice, and contributions of our fellows during the pandemic. The institutional response is a shared mission, with both faculty and trainees jointly contributing wherever service has been needed. Informal weekly IVC check-ins and “happy hours” help maintain program cohesion. Social networks, even when remote, have been demonstrated to alleviate not just immediate anxiety but also long-term distress (12, 13). During infectious disease outbreaks, organizational support has been shown to protect the mental health of healthcare staff (14).

The Graduate Medical Education Committee at the Johns Hopkins University has provided extensive wellness resources, extending from free mindfulness apps to mental health counseling. Housing assistance has been made available for providers unable to live at home because of quarantine restrictions or family members at high risk for complications from COVID-19 infection. Advance planning, crowdsourcing, and good resource stewardship have fortunately afforded trainees the necessary PPE to enable an appropriately safe work environment.

Safety helps create an environment conducive to learning. Unfortunately, physically safe learning and work environments have not been possible for all training programs during the COVID-19 pandemic. In those situations, IVC could allow programs currently less challenged by an influx of COVID-19 patients to share educational content with trainees at more heavily constrained institutions.

The crisis of COVID-19 has undoubtedly brought major challenges to clinical care and education in fellowship training. Technology can be leveraged to support trainee education during periods of physical distancing, heavy clinical workload, and heightened stress. Although the concept of bedside teaching espoused by Osler has been restructured during COVID-19, we now have an opportunity to engage new participants and other programs in a way not previously emphasized. The eventual benefit to nephrology education rests in once again physically connecting to our patients and colleagues while maintaining a newfound inclusivity. By moving apart, we may ultimately come closer together. ■

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# Post-COVID-19 Dialysis Poses Challenges for Dialysis Providers and Patients

By Bridget M. Kuehn

As the first wave of survivors of severe COVID-19 begin to leave hospitals, many face a new challenge—dialysis.

Acute kidney injury (AKI) is recognized as a common complication in patients who develop severe COVID-19 infections requiring intensive care. Among those who recover enough to be discharged from the hospital, between 20% and 90% may require dialysis, according to reports from around the country, said Jeffrey Silberzweig, MD, co-chair of the ASN COVID-19 Response team, during a recent ASN webinar (1).

“We need to anticipate a surge of these patients,” Silberzweig said.

The Dialysis After Discharge: Transitions of Care For COVID-19-Positive Patients webinar brought together experts from around the country to discuss the challenges facing these patients and the steps dialysis providers should take to help them.

Transportation to dialysis is a major concern for patients who are COVID-19 positive because they cannot take public transportation or use a van service or ambulette, Watson noted. They can take an ambulance. But it may only be covered by Medicare for patients who are non-ambulatory. Ambulance availability also may be limited in COVID-19 hotspots.

Financial stress for newly discharged COVID-19 patients, as well as all dialysis patients, is a concern now and in coming months, Watson noted. They may be unable to work or have family members laid off during the pandemic. “This will affect their ability to get their prescriptions, to get transportation to and from dialysis, and even [meet] very basic needs of food and shelter,” he said. Uninsured patients who developed AKI as a complication of COVID-19 also do not qualify for Medicare coverage for outpatient dialysis.

Nephrologists also face the challenge of deciding when it is appropriate to certify these patients with end stage renal

There are some barriers, Srivatana noted. For example, currently the Centers for Medicare & Medicaid Services (CMS) does not reimburse for telehealth PD training. But the Special Purpose Renal Dialysis Facility designation from CMS has expanded dialysis options for COVID-19 patients. For example, it can be used by dialysis centers with PD programs to simultaneously treat and train patients before transitioning them home, he said.

Few skilled nursing facilities have the capacity to offer PD. A CMS waiver will allow home PD nurses to provide care in these settings, Srivatana said, though they would have to find coverage for their regular home patients.

“We must do better across the United States to have PD capability in our skilled nursing facilities and long-term care facilities and provide safe and quality care in these facilities,” Naljayan said.

Another concern is that PD is associated with higher rates of readmission (6), Naljayan noted, which may be of particular concern among COVID-19 patients who may experience both weakness and cognitive difficulties after discharge. It is important these patients be assessed prior to discharge to determine if they are a good candidate for home dialysis. He also recommended a virtual home visit to assess their home environment.

“These patients are at a very high risk for readmission and they’re extremely frail, so close monitoring with frequent assessments and communication with the team and the physician will be needed to keep these patients from going back into the hospital,” he said. Periodic assessments by a social worker may also be necessary to ensure that it is safe for the patient or their caregiver to continue home PD.

Telehealth has proved to be a critical tool for facilitating home PD during the pandemic, Srivatana said. This has been particularly important in hotspots like New York City where patients would likely have to brave public transportation for inpatient visits.

“My own patients have found this option very, very satisfying as they’re extremely reluctant to leave their homes and come to clinics or offices,” Srivatana said.

Naljayan said telehealth may also facilitate the frequent check-ins necessary to ensure patients remain safe doing home PD. Srivatana predicted that increased use of telehealth to reduce unnecessary visits may be here for some time given the uncertainty about how long the pandemic and associated precautions will last.

“This is a challenge, but also an opportunity to rethink the way we do things,” Srivatana said. ■



## Post-recovery transitions

Care transitions under normal circumstances can be “fraught with disaster,” noted Thomas Watson, MD. For example, confusion about medications or missed doses or transportation problems can lead to serious problems, he said. But these transitions may be even more challenging for patients who are recovering from COVID-19.

“One of the bewildering issues we currently face, is that we just don’t know a lot [about the disease],” Watson said. For example, there are questions about how long a patient who has been COVID-19 positive remains infectious and whether they are immune to the SARS-CoV-2 virus after infection. The CDC has created guidelines (2) for dialysis facilities on isolation for COVID-19 patients and staff, as well as recommendations for screening, mask use, and disinfection policies during the pandemic. These precautions have also been addressed in previous ASN webinars (3).

Many COVID-19 patients leave the hospital debilitated after prolonged hospitalization, Watson noted. They may need staff assistance to get to their chair in an outpatient dialysis facility. They may require more frequent check-ins or follow-up testing for hypoxia or blood clots. They may need dietitian support to treat protein or calorie malnutrition or administration of oral nutritional supplements onsite, which may be difficult in dialysis facilities where masks are required. Many will be admitted to rehabilitation or skilled nursing facilities requiring additional transitions in care.

“Each of these transitions we have to worry about making sure their medications are appropriate, we have to worry about making sure they are appropriately set up for transportation to get their life-sustaining dialysis treatments,” Watson said.

disease and begin planning for vascular access or a potential home dialysis modality. Watson explained it is not yet clear how many patients with COVID-19-related AKI will recover normal kidney function, although he expected more data will be available soon.

“It’s probable that they won’t recover as frequently as someone who had AKI related to a different type of infection,” he said.

In fact, nephrologists from hard hit Louisiana and New York City estimated during the web briefing that only 10% to 15% of patients with COVID-related AKI will recover kidney function based on their experience so far. Mihran Naljayan, MD, acting chief of nephrology and hypertension and associate professor of clinical medicine at the Louisiana State University School of Medicine in New Orleans explained that patients who require intensive care for COVID-19 are extremely ill; in fact 70% to 80% do not survive. Among those who do survive, those who had fewer health problems prior to COVID-19 are the most likely to recover kidney function, said Vesh Srivatana, MD, director of peritoneal dialysis at the Rogosin Institute in New York City.

## Peritoneal dialysis in demand

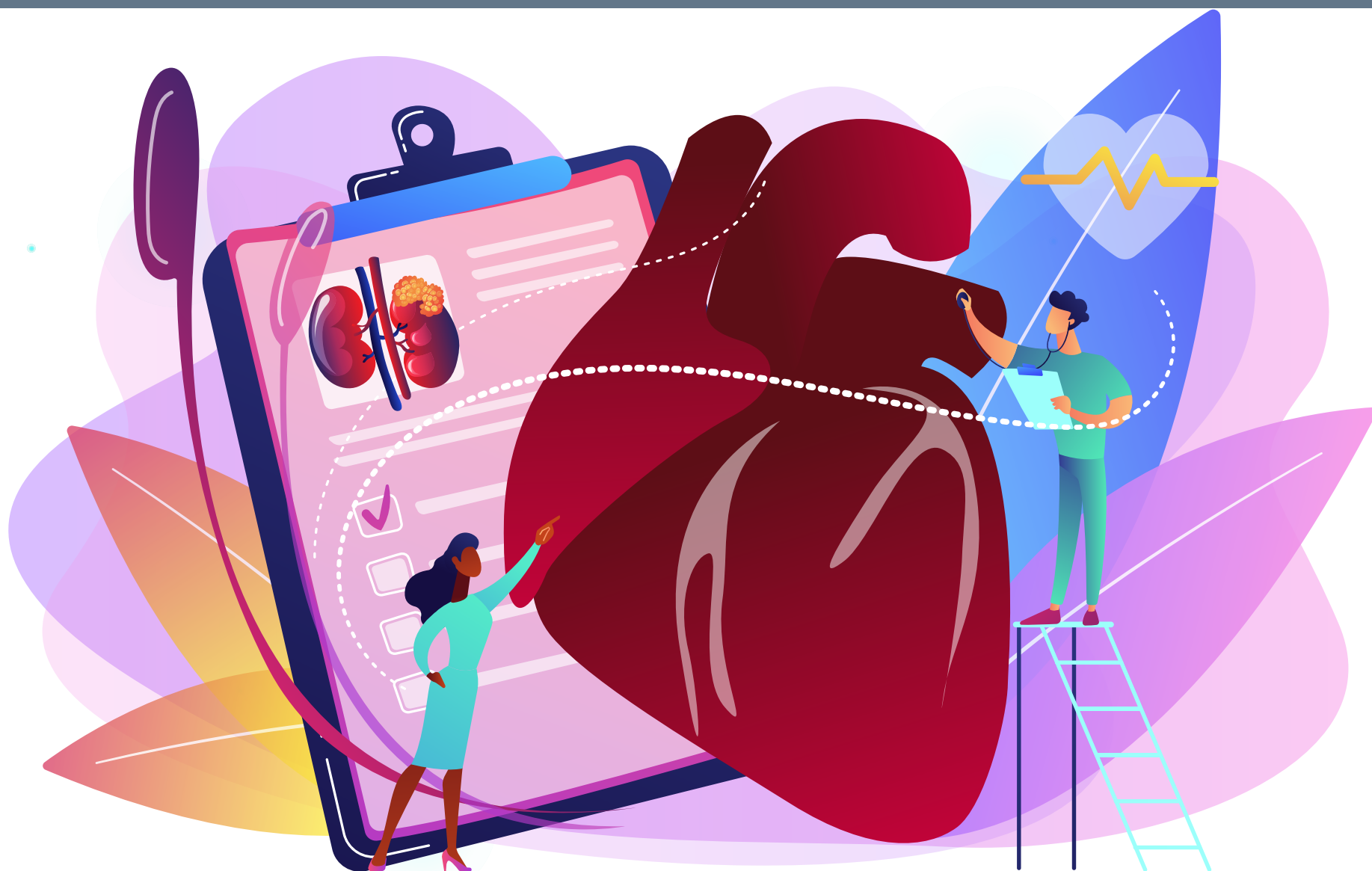
Peritoneal dialysis (PD) is emerging as an appealing option for COVID-19 survivors requiring dialysis after discharge. Acute PD has been associated with improved rates of kidney recovery (4), and it preserves residual kidney function better than hemodialysis (5), noted Naljayan. It can also allow patients to avoid complications associated with a hemodialysis catheter and allow home dialysis.

“In COVID-19 hotspots in the US, traditional dialysis resources have been stretched thin and that’s caused a recent surge in interest and use of acute PD,” Srivatana said.

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# CARDIOVASCULAR DISEASE and the Kidney

By Mohammed Elsadany, Yifeng Yang, Sonali Gupta, and Joseph Mattana

It has been well known for many years that cardiovascular disease disproportionately affects patients with chronic kidney disease (CKD) and kidney failure, both through acceleration of atherogenesis as a consequence of reduced kidney function and through the various comorbidities with which our patients are frequently afflicted. Despite growing mechanistic insights into kidney–heart interactions, atherogenesis, cardiac hypertrophy, valvular heart disease, and other phenomena and into new therapies that are available, patients with kidney disease continue to experience an excessive burden of cardiovascular disease and events.

Cardiovascular disease, particularly coronary artery disease, is more often a condition of the older individual, but several recent reports have painfully reminded us that cardiovascular disease and its devastating consequences in the patient with kidney disease starts early, with increases in cardiovascular mortality beginning in childhood and continuing through young adulthood (1, 2). Of note, this increased mortality is found not only in young adults in whom kidney disease developed in childhood but also in those in whom it developed later, during the young adult years; this emphasizes that cardiovascular disease may develop rapidly in the setting of kidney disease. An additional sobering thought is that whereas normalization or near-normalization of kidney function with transplantation has innumerable salutary effects, the cardiovascular disease burden experienced by the patient continues after transplantation, and ongoing vigilance and aggressive management are essential.

Fortunately, as our mechanistic understanding of these relationships has grown, we have learned over the years that our patients can also benefit from many of the therapies that are provided to patients without kidney disease. Statin drugs, for example, constitute one such therapy, but as we are reminded in an article in this issue, the benefits of statins are less with more advanced kidney disease, and questions remain as to why this is so. Coronary artery bypass grafting and percutaneous coronary interventions, including stent deployment, are used successfully on a regular basis in patients with CKD and kidney failure.

In this issue, we highlight several of the more recent cardiovascular interventions and their impact in patients with kidney disease. Although it is not unexpected that such therapies may be more challenging to implement in the patient with kidney disease, there

are data that such therapies, in addition to prolonging survival, may in some cases lead to improvements in kidney function, with the potential to forestall the development of kidney failure. Both transcatheter aortic valve replacement (TAVR) and mitral valve clipping (MitraClip) have been used in patients with kidney disease and are two such recent procedural examples.

In addition to procedural interventions such as TAVR and MitraClip, as noted in this issue, newer medical therapies also hold promise for patients with kidney disease. One such example is represented by the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. As a consequence of inhibition of PCSK9, LDL receptor numbers on the hepatocyte surface increase, promoting LDL uptake and subsequently suppression of LDL synthesis. Although data at this time are limited, especially in patients with more advanced kidney disease, this new class of agents merits further study and hopefully may find a place among the therapeutic medical options for reducing the morbidity and mortality related to cardiovascular disease.

All nephrologists are well aware of the high incidence of cardiovascular disease in the kidney disease population. Ongoing research is urgently needed to further our understanding and pursue new therapies to help us better manage and hopefully prevent this vexing problem. ■

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# Transcatheter Aortic Valve Replacement and the Kidney

By Mohammed Elsadany, Yifeng Yang, Sonali Gupta, and Joseph Mattana

Until recently, transcatheter aortic valve replacement (TAVR) has been a treatment option for patients with severe symptomatic aortic stenosis who are not candidates for surgical aortic valve replacement (SAVR). It has been used for patients who are at high or intermediate surgical risk, but recent studies have demonstrated the noninferiority and also superiority of TAVR compared with SAVR in patients at low surgical risk (1), and TAVR has found a role in patients with kidney disease as well. The number of TAVR procedures is therefore expected to grow. Whereas kidney disease may have an impact on TAVR outcomes, the effects of TAVR on the kidney encompass several topics, which will be discussed here.

## TAVR and AKI

Acute kidney injury (AKI) is one of the important complications of TAVR, with a reported incidence ranging from 6% to 57% (2–10). Patients undergoing TAVR often have multiple comorbidities contributing to an increased AKI risk, such as chronic kidney disease (CKD), hypertension, diabetes mellitus, chronic obstructive pulmonary disease, peripheral vascular disease, congestive heart failure, higher EuroSCORE, and older age (3, 4, 6, 8–11). Intraoperative risk factors for AKI after TAVR include hypotension, use of an intra-aortic balloon pump, procedural bleeding events, blood transfusion, use of nephrotoxic contrast media, and the transapical approach (3, 4, 6, 7). Postoperative risk factors for AKI include hemodynamic instability and congestive heart failure.

As expected, AKI after TAVR is associated with worse outcomes (6–10). In one study, patients who experienced AKI had higher in-hospital mortality (21% vs. 4%,  $p = 0.007$ ) and 30-day mortality (29% vs. 7%,  $p = 0.004$ ) in comparison with patients without AKI (7). Another study showed that post-TAVR AKI development is associated with increased in-hospital mortality (odds ratio 4.74, 95% confidence interval 1.39–18.48) and 6-month mortality (odds ratio 4.66, 95% confidence interval 2.32–9.63) (6).

Although some studies have shown that TAVR entails a higher risk for AKI than does SAVR, this may be confounded by selection bias, with patients with more comorbid conditions and therefore higher AKI risk being selected for TAVR rather than SAVR (12). A propensity-matched study, in fact, showed no significant difference in the incidence of postoperative AKI (11). In addition to measures such as avoidance of hypovolemia and intraprocedural hypotension and minimizing exposure to radiocontrast media, the PROTECT-TAVI study found that use of the RenalGuard System was associated with a reduced incidence of AKI in comparison with a control group who received normal saline solution (5.4% vs. 25.0%,  $p = 0.014$ ) (13). Given the adverse impact of AKI, it is of course important to identify those patients who are at high risk for post-TAVR AKI and to use measures to help prevent this serious complication.

## TAVR and CKD

CKD is a risk factor for the development of post-TAVR AKI and for increased length of stay and mortality (14–16). A meta-analysis found that patients with CKD and high surgical risk undergoing TAVR had an increased risk of short-term and long-term mortality (hazard ratio 1.51, 95% confidence interval 1.22–1.88; and hazard ratio 1.56, 95% confidence interval 1.38–1.77, respectively,  $p < 0.01$ ).

However, no association was found between CKD and mortality in low- to intermediate-risk patients (14). Another study reported that those with CKD had significantly increased in-hospital mortality compared with non-CKD/ESRD patients (4.5% vs. 3.7%, adjusted odds ratio 1.34, 95% confidence interval 1.20–1.31,  $p < 0.001$ ) (15). That same study found that CKD was associated with an increased length of hospital stay, hemorrhage requiring transfusion, and need for permanent pacemaker implantation ( $p < 0.001$ ) (15). In another study, a total of 540 patients undergoing TAVR were divided into three groups according to GFR before TAVR: group A, normal renal function, i.e., GFR  $\geq 60$  mL/min; group B, impaired renal function, i.e., GFR 30–59 mL/min; and group C, severely impaired renal function, i.e., GFR  $< 30$  mL/min. Multivariate analysis showed that GFR had a significant impact on mortality ( $p < 0.0008$ ). Subgroup analysis revealed a significant difference in mortality rates between the three groups at 30 days: (group A, 5.4%; group B, 9.0%; and group C, 25.0%) and at 12 months (group A, 15.0%; group B, 32.0%; and group C, 49%) (17).



**TAVR has become a valuable option for the treatment of severe aortic stenosis in patients with CKD and in those with ESRD receiving renal replacement therapy, although caution must be exercised because the outcomes are less favorable than in the general population.**

Despite the finding that CKD is associated with higher mortality after TAVR, patients with CKD nevertheless appear to clearly benefit from interventions to treat aortic stenosis. In one study of patients with CKD, aortic valve replacement (AVR) was associated with improved survival (time-dependent hazard ratio 0.63, 95% confidence interval 0.45–0.88,  $p = 0.006$ ) (18), although the majority of

the patients underwent SAVR. Another study that used the National Inpatient Sample reported lower in-hospital mortality and lower rates of AKI, dialysis requiring AKI, and postoperative stroke and also shorter lengths of stay and a nonsignificant difference in cost for CKD patients undergoing TAVR in comparison with SAVR (19).

Although CKD may increase the risk of AKI and other complications in patients undergoing TAVR, there is great interest as to whether TAVR may have a favorable impact on GFR, given its potential to improve arterial filling and renal perfusion among other physiologically relevant consequences. In the study described above (17), it was in fact noted that patients with moderately impaired renal function (group B) demonstrated an increase in GFR (46.17 mL/min vs. 55.72 mL/min,  $p < 0.0001$ ), and patients with severely impaired renal function (group C) also demonstrated an increase in GFR (19.54 mL/min vs. 27.9 mL/min,  $p < 0.0001$ ). The increase in GFR was noted in a total of 301 patients (55.7%). The cardiac output of these patients showed a significant increase after TAVR (17). Given these findings, although TAVR carries an increased risk for AKI in CKD patients, it also may lead to improvement in kidney function, likely because of improved cardiac output after replacement of the diseased valve.

## TAVR and ESRD

ESRD is associated with higher mortality after TAVR (15, 16). Patients with ESRD have been reported to have significantly increased in-hospital mortality in comparison with non-CKD/ESRD patients (8.2% vs. 3.7%, adjusted odds ratio 2.51, 95% confidence interval 2.02–3.12,  $p < 0.001$ ) and an increased length of hospital stay, more episodes of hemorrhage requiring transfusion, and greater need for permanent pacemaker implantation ( $p < 0.001$ ) (15). Another study compared TAVR outcomes between dialysis and nondialysis patients and found the dialysis group to have increased mortality at 30 days (13% vs. 6%,  $p < 0.01$ ). Multivariable regression revealed that dialysis was independently associated with worse survival after TAVR (hazard ratio 1.73, 95% confidence interval 1.33% to 2.25%,  $p < 0.01$ ) (20). In comparison with a propensity-matched group of dialysis patients who underwent SAVR, dialysis patients who underwent TAVR had significantly shorter hospital stays and comparable survival (20).

A study that used the National Inpatient Sample between 2012 and 2014 compared in-hospital outcomes of TAVR versus SAVR in ESRD patients undergoing hemodialysis and showed that the in-hospital mortality rate was similar between TAVR and SAVR (8% vs. 10.3%,  $p = 0.58$ ). Compared with SAVR, TAVR was associated with shorter length of stay (8 vs. 14 days,  $p < 0.001$ ), lower hospitalization cost (\$276,448 vs. \$364,280,  $p = 0.01$ ), fewer in-hospital complications (60.6% vs. 76%,  $p = 0.003$ ), and a higher rate of discharge to home (31.4% vs. 17.7%,  $p = 0.004$ ) (21).

Whereas ESRD is associated with higher mortality after TAVR, just as for CKD patients ESRD patients do benefit substantially from AVR. For example, a study that used a Japanese multicenter registry reported that patients using hemodialysis who underwent AVR experienced lower mortality than did those receiving conservative treatment (22). The cumulative 5-year all-cause mortality was 60.6% in the AVR group versus 75.5% in the conservative group ( $p < 0.001$ ), and sudden death was 10.2% in the AVR group versus 31.7% in the conservative group ( $p < 0.001$ ) (22), which suggests that hemodialysis patients also benefit from interventions to treat aortic stenosis.

## Conclusions

TAVR has become a valuable option for the treatment of severe aortic stenosis in patients with CKD and in those with ESRD receiving renal replacement therapy, although caution must be exercised because the outcomes are less favorable than in the general population. As for CKD, al-



though it may increase the risk for development of AKI, the potential benefits of TAVR appear to include the possibility that it may ultimately result in an increase in GFR and improve the survival rate. Recently, emerging data on the preferential use of TAVR in low-surgical-risk patients will be important to examine in patients with kidney disease as well. ■

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# TRANSCATHETER MITRAL VALVE REPAIR (MitraClip) and the Kidney

By Mohammed Elsadany, Yifeng Yang, Sonali Gupta, and Joseph Mattana

**T**ranscatheter mitral valve repair (TMVR) is a minimally invasive procedure used as a treatment option for patients with symptomatic chronic moderate to severe, or severe mitral regurgitation (MR). The MitraClip is an edge-to-edge leaflet repair device and is currently the only device approved by the U.S. Food and Drug Administration for TMVR. MR is one of the most common valve lesions. Patients with chronic kidney disease (CKD) and MR usually have multiple comorbidities, increasing their surgical risk for valve replacement and making them possible candidates for TMVR by use of the MitraClip. The interaction between MR and the kidney is complex: MR can lead to abnormalities in hemodynamics and congestive heart failure, which may lead to or worsen CKD. Repair of the mitral valve may therefore be expected to have a favorable impact on kidney function in some patients. Conversely, kidney function plays an important role in cardiovascular disease, and it is well known that the outcomes of many procedures such as transcatheter aortic valve replacement (TAVR) are worse in patients with CKD than in the general population. Here we review the use of MitraClip and its application in patients with kidney disease.



## MitraClip and CKD

Given the interrelationships between the heart and kidneys, it is plausible that repair of the mitral valve, including repair performed by the transcatheter approach, might have a favorable impact on kidney function in some patients in whom a component of the kidney disease is a consequence of decreased effective arterial volume.

In one such study (1), 854 patients with moderate to severe or severe MR (3+ or 4+, respectively) who underwent TMVR with the MitraClip device in multicenter investigational trials (2, 3) and the REALISM (Real World Expanded Multicenter Study of the MitraClip® System) continued access registry were evaluated. The distribution of the estimated GFRs (eGFRs) of the patients at the baseline of the study was as follows: CKD

stage 1 or 2 (eGFR  $\geq 60$  mL/min per 1.73 m<sup>2</sup>), n = 438; CKD stage 3 (eGFR 30–59 mL/min per 1.73 m<sup>2</sup>), n = 364; and CKD stage 4 (eGFR  $< 30$  mL/min per 1.73 m<sup>2</sup>), n = 52. Follow-up evaluation after 1 year revealed improvements in eGFR in patients with more advanced CKD. In the overall cohort with paired baseline and 1-year data (n = 579), the mean change in eGFR was  $-1.0 \pm 15.2$  mL/min per 1.73 m<sup>2</sup> (p = 0.10). For patients with CKD stage 1 or 2 at baseline (n = 319), the eGFR was decreased 1 year after the procedure ( $-4.1 \pm 16.6$  mL/min per 1.73 m<sup>2</sup>). However, among patients with CKD stage 3 at baseline (n = 227), the mean eGFR increased ( $+2.6 \pm 12.4$  mL/min per 1.73 m<sup>2</sup>), and among patients with CKD stage 4 or 5 at baseline (n = 33), this

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## Transcatheter Mitral Valve Repair

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increase in eGFR was even greater ( $+4.8 \pm 9.5$  mL/min per  $1.73 \text{ m}^2$ ). When examined by CKD stage, 36.4% of patients with CKD stage 4 or 5 at baseline were found to have improved to CKD stage 3 1 year after the MitraClip procedure. When the clinical characteristics of patients who experienced improvement in kidney function (defined as increase in eGFR  $\geq 5$  mL/min per  $1.73 \text{ m}^2$  at 1 year) were compared with those who did not, only New York Heart Association class 3 or class 4 at baseline were independently associated with this degree of improvement in eGFR (odds ratio 2.2, 95% confidence interval 1.41–3.57,  $p = 0.007$ ). These findings suggest that TMVR with the MitraClip has the potential to improve the eGFR in some patients with more advanced CKD, especially when the latter is related to heart failure.

As with transcatheter aortic valve replacement (TAVR), an important question about TMVR with the MitraClip is whether CKD has an impact on mortality. An unadjusted analysis done in the same study (1) indeed showed that the 1-year survival rate was associated with baseline kidney function. The mortality rate at 1 year was 15.0% for the overall cohort. When stratified by stage of CKD, mortality rates were found to be 9.0%, 20.6%, and 26.0% among patients with CKD stage 1 or 2, stage 3, and stage 4 or 5, respectively ( $p < 0.001$ ).

either moderate CKD (stage 3,  $n = 91$  [80.5%]) or severe CKD (stage 4,  $n = 22$  [19.5%]). EuroSCORE II and the Society of Thoracic Surgery score were higher in the CKD group. Patients were followed up for 1 year after the procedure. The primary safety endpoint was the incidence of major adverse events and was higher in the CKD group than in the group without CKD (12.4% vs. 2.0%,  $p = 0.003$ ). The primary efficacy endpoint (freedom from death, surgery for mitral valve dysfunction, or grade  $\geq 3+$  MR at 12 months) was significantly lower in the CKD group than in the no-CKD group (65.8% vs. 84.2%, log-rank  $p = 0.005$ ). Baseline CKD was found to be an independent predictor of the primary efficacy endpoint (adjusted hazard ratio 2.48, 95% confidence interval 1.29–4.79,  $p = 0.006$ ).

An additional study showed that CKD is associated with worse outcomes in patients undergoing TMVR with MitraClip (6). In that study, 212 consecutive patients who underwent TMVR with MitraClip were enrolled and were divided into three groups. The groups had normal eGFR (60 mL/min per  $\text{m}^2 \leq \text{eGFR}$  in 70 patients (34%), mild CKD (30 mL/min per  $\text{m}^2 \leq \text{eGFR} < 60$  mL/min per  $\text{m}^2$  in 106 patients (51%), and severe CKD ( $\text{eGFR} < 30$  mL/min per  $\text{m}^2$  in 30 patients (15%). The median follow-up period was  $475 \pm 425$  days. Patients in the CKD groups were older, had higher logistic EuroSCOREs, and higher N-terminal pro B-type natriuretic peptide levels than did those in the normal eGFR group. Univariate Cox regression analysis showed that severe CKD was associated with an increased risk

sis patients ( $p < 0.001$ ). Hence, this study also demonstrates that CKD is associated with worse outcomes after MitraClip.

Whereas the outcomes after MitraClip are worsened by the presence of CKD, an important question is how such patients would fare without the procedure being performed. Although direct comparisons are not available for patients with CKD who receive MitraClip compared with no procedural intervention, several inferences can perhaps be drawn. In the general population, the annual mortality rate for medically treated patients with primary severe MR is up to 6%, and intervention by mitral valve replacement or repair is well known to be associated with an improved survival rate and reduced symptoms (8). Patients with MR and CKD appear to have far worse survival rates than do those without CKD, as evidenced in one study in which the 5-year survival rate of patients with severe MR and CKD was 37%, compared with 65% for severe MR without CKD (9). Hence, although outcomes with MitraClip in patients with CKD are less favorable than in those without CKD, it seems likely that this is outweighed by a reduction in the mortality rate that would be found in the absence of such intervention. ■

### Conclusions

In a manner similar to what has been observed with TAVR, CKD is associated with worse outcomes in patients undergoing MitraClip placement, including higher mortality rates compared with non-CKD patients. Among the benefits of MitraClip, some patients with CKD experience an improvement in their kidney function after MitraClip placement, likely as a result of improved effective arterial volume. Our growing understanding of these relationships can help us best select the patients who can benefit significantly from this procedure.

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**Given the interrelationships between the heart and kidneys, it is plausible that repair of the mitral valve, including repair performed by the transcatheter approach, might have a favorable impact on kidney function in some patients in whom a component of the kidney disease is a consequence of decreased effective arterial volume.**

Another multicenter study demonstrated an association between CKD and worse outcomes. That study used a multicenter registry of 173 patients treated with MitraClip between 2009 and 2012 at three centers (4). The patients were divided into three groups: advanced CKD (creatinine clearance [CrCl]  $< 30$  mL/min, group 1,  $n = 20$ ), moderate CKD (CrCl 30–60 mL/min, group 2,  $n = 78$ ) and normal kidney function (CrCl  $> 60$  mL/min, group 3,  $n = 75$ ). Only 1 patient in group 1 was using dialysis. Patients with advanced CKD were significantly older and had higher values on the logistic EuroSCORE. There was no significant difference in the procedural success rate among the three groups. Data for all-cause mortality (16.2%) and readmissions due to heart failure (10%) with a mean follow-up time of  $16.2 \pm 11.1$  months were available in 130 patients (17 patients in group 1, 61 patients in group 2, and 52 patients in group 3). Mortality rates differed significantly between the groups (52.9% for group 1, 8.2% in group 2, and 13.5% in group 3,  $p < 0.001$ ). With regard to a combined endpoint of death or readmission due to heart failure, a significant difference between the groups was noted, with advanced CKD (group 1) being identified as an independent predictor of the combined event (hazard ratio 4.8, 95% confidence interval 1.1–21.3,  $p = 0.04$ ).

Another study assessed the impact of CKD on the clinical outcomes of MitraClip with up to 12 months of follow-up. In that study, 214 patients undergoing TMVR with MitraClip were included (5). The patients were divided into two groups: baseline CKD ( $n = 113$ ) or no CKD ( $n = 101$ ). Patients with baseline CKD had

for all-cause death ( $p = 0.002$ , hazard ratio 3.423), and multivariable Cox regression analysis also revealed an association between severe CKD and all-cause death ( $p = 0.001$ , hazard ratio 4.322).

The authors also evaluated the impact of MitraClip on kidney function among the study patients (6). Kidney function data after 6 months were available for 81 patients. Three of the patients were using hemodialysis and were excluded, and 78 patients were studied. Improvement of kidney function was noted in 22 patients (28%). In addition, among the patients whose kidney function improved after MitraClip placement, the long-term survival rate was significantly higher than in the patients whose kidney function did not improve ( $p = 0.028$ ).

A recent study of MitraClip and kidney function used the National Cardiovascular Data Registry Transcatheter Valve Therapy Registry (7). In that study, 5213 patients who underwent the MitraClip procedure were evaluated. CrCl was  $< 60$  mL/min in 77% of patients ( $n = 4010$ ) and  $< 30$  mL/min in 23% ( $n = 1183$ ) of patients. The primary outcome was a composite of all-cause mortality, stroke, and new requirement for dialysis. The rates of the primary outcome were higher in patients with lower CrCl, occurring in 1.4% of those with CrCl  $> 60$  mL/min, 2.7% of those with CrCl 30 to  $< 60$  mL/min, 5.2% of those with CrCl  $< 30$  mL/min, and 7.8% of dialysis patients ( $p < 0.001$ ). Following a similar pattern, patients with lower CrCl had higher 1-year mortality rates, with a rate of 13.2% of those with CrCl  $> 60$  mL/min, in 18.8% of those with CrCl 30 to  $< 60$  mL/min, in 29.9% of those with CrCl  $< 30$  mL/min, and in 32.3% of dialy-



# STATIN DRUGS IN CKD AND ESRD: **What Is Their Role?**

By Yifeng Yang, Mohammed Elsadany,  
Sonali Gupta, and Joseph Mattana

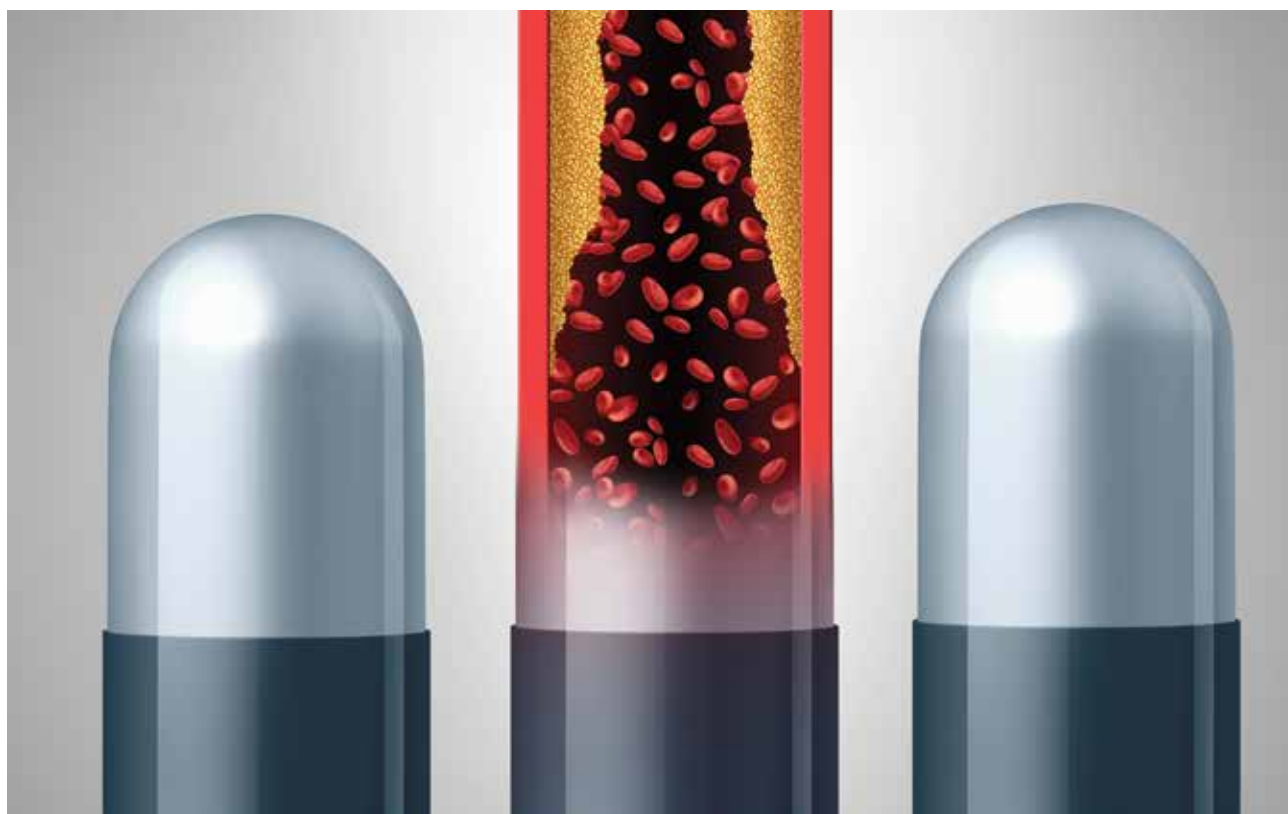
**D**yslipidemia has long been established as a traditional risk factor for cardiovascular disease in the general population. Dyslipidemia, characterized especially by elevated LDL and VLDL, is well known to be associated with higher atherosclerotic cardiovascular disease risk and is a large public health threat.

In patients with chronic kidney disease (CKD) and end stage renal disease (ESRD), cardiovascular disease is accelerated with an even larger impact, compared with the general population. Multiple variables are thought to contribute to this heightened propensity to and accelerated course of cardiovascular disease, including significant alterations in lipoprotein metabolism such as decreased HDL and increased VLDL, vascular damage promoted by uremia-associated inflammation, oxidative stress, and endothelial dysfunction. Microalbuminuria itself, even without diabetes or impaired kidney function, is associated with the development of cardiovascular disease and higher mortality. For patients with ESRD who are using dialysis, their mortality from cardiovascular disease is 10 to 30 times higher than that in the general population.

The well-known 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins) can effectively reduce serum LDL levels and have been demonstrated to improve major cardiovascular outcomes and reduce mortality, thus providing these drugs with a major role in the prevention of primary and secondary cardiovascular disease (1). Whereas CKD is a risk factor for accelerated atherogenesis and cardiovascular events, the role of statins is well known to be complex. In patients with CKD stages 1–4, many studies have shown that statins can in fact prevent cardiovascular events. In 2011, the Study of Heart and Kidney Protection (SHARP) trial found a 17% reduction in major cardiac events in the statin-treated group than in the group receiving placebo (2). Subsequently, a meta-analysis by Major et al. (3), including six clinical trials with more than 8000 patients, found that statins reduced the risk of cardiovascular disease by 41% in patients with CKD stages 1–3, including mortality, coronary heart disease events, and stroke. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines thus recommend the use of a statin or a statin/ezetimibe combination for patients with CKD who are older than 50 years and do not require dialysis.

As the CKD stage advances, the benefit of statins on cardiovascular outcomes unfortunately appears to decrease. Using a Health Insurance Research Database, Huang et al. (4) studied >14,000 nondiabetic, CKD stage 5 (estimated GFR <15 mL/min per 1.73 m<sup>2</sup>), and predialysis patients. Among them, statin users were identified and were matched to non-statin users with propensity scoring. The investigators found that statin therapy did not appear to decrease the risk of de novo major cardiovascular events in patients with advanced kidney disease, although it was associated with reduced all-cause mortality and sepsis-related mortality.

For patients using either hemodialysis or peritoneal dialysis, statins unfortunately do not appear to be beneficial in reducing cardiovascular events. In 2012, Palmer et al. (5) published a meta-analysis incorporating 80 clinical trials with more than 51,000 participants. They found moderate- to high-quality evidence demonstrating that statins had little or no effect on all-cause mortality, cardiovascular mortality, or cardiovascular events in patients using dialysis. Another me-



ta-analysis of 28 trials and more than 180,000 participants showed that smaller relative effects on major vascular events were observed as estimated GFR declined, and little evidence of benefit was found for patients using dialysis (6). Given these data, the KDIGO guidelines state that initiation of statin treatment is not recommended for hemodialysis patients.

Why do the cardiovascular-protective effects of statins grow smaller as the estimated GFR declines in CKD patients? It has been proposed that the progression of cardiovascular disease in this population may be related more to other lipoproteins, for example, intermediate-density lipoprotein. However, statins, specifically pravastatin, can reduce both intermediate-density lipoprotein and LDL cholesterol concentrations to a similar extent, making this theory somewhat less plausible. Others have proposed that other pathophysiologic processes such as inflammation and arterial wall calcification are more dominant than derangements of LDL metabolism itself. Although statins do have well-known anti-inflammatory effects, in the face of multiple variables that can contribute to vascular wall damage, their efficacy may be consequently blunted. An additional hypothesis is that the level of lipids in the blood may be of lesser importance than intracellular accumulation and that altered expression of cholesterol transport genes promoting a lipid-accumulation phenotype in macrophages may be operative (7).

The role of statins in patients with kidney disease extends beyond cardiovascular protection. A meta-analysis by Navaneethan et al. (8) involving 26 studies and more than 25,000 participants showed that in CKD patients not using dialysis, statins may reduce urine protein excretion, although the authors did not find an impact on the rate of decline in kidney function. Chung et al. (9) carried out a retrospective analysis using a National Health Insurance Research Database in Taiwan and found during a follow-up period of approximately 3 years that statin therapy may reduce the risk of development of ESRD in patients with predialysis advanced CKD. An additional study using this same database revealed that statin use may be associated with a decreased risk for the development of atrial fibrillation/flutter in CKD patients, although, as with the prior study, it is at present unclear to what extent these findings may be applicable to other patient populations (10).

In summary, whereas statins appear to have less of an impact on primary prevention of cardiovascular events, with greater declines in GFR, it is critical to remember that they can benefit many patients with earlier-stage CKD. Other potential effects of statins in patients with kidney disease, such as possibly reducing proteinuria, slowing progression, and decreasing atrial tachyarrhythmias, merit further study. ■

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## EMERGING THERAPIES FOR CARDIOVASCULAR DISEASE: PCSK9 Inhibitors and Their Potential Role in Patients with CKD

By Mohammed Elsadany, Yifeng Yang, Sonali Gupta, and Joseph Mattana

Patients with chronic kidney disease (CKD) are at higher risk for premature cardiovascular disease and events in comparison with the general population. This appears to result from a complex interplay of various metabolic and vascular factors. There are some underlying differences in the lipid profile of CKD patients versus individuals without CKD. Among them are an abundance of small, dense, atherogenic LDL particles; elevated concentrations of triglycerides; reduced HDL cholesterol concentrations; altered lipoproteins; and the presence of lipoprotein and chylomicron remnants—findings that are characteristic of the lipid profile in this population. Among other variables that affect the heightened propensity of CKD patients to cardiovascular disease are increased oxidative stress, vascular calcification, and the adverse impact of common comorbid conditions, including diabetes mellitus and hypertension.

Statins and ezetimibe are recognized as the main cholesterol-lowering drugs. Although post hoc analyses of several large clinical trials have shown the efficacy of statins in reducing cardiovascular deaths in the CKD population (not using dialysis) with a magnitude of benefit similar to that in the general population, these trials suffered from under-representation of this subset of the population and the exclusion of patients with advanced kidney disease (1). Moreover, most statins are renally cleared, and the risk of drug–drug interaction in CKD patients limits the use of high-intensity statins in this population subset.

More recently, the newer cholesterol-lowering drugs that are proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (evolocumab and alirocumab) have been approved for the control of dyslipidemia in high-risk populations when standard lipid-lowering therapies fail to sufficiently reduce LDL cholesterol levels. PCSK9 binds to the LDL receptor on hepatocytes, resulting in lysosomal degradation of the PCSK9/LDL receptor complex, thereby promoting increased LDL levels and LDL synthesis. Inhibition of PCSK9 results in increased recycling of the LDL receptor to the cell surface, which promotes the removal of LDL cholesterol particles from the circulation, thereby lowering LDL cholesterol concentrations while suppressing LDL synthesis. Of note, PCSK9 is also transiently expressed in the kidneys and is thought to play a role in renal development. Podocyte damage is observed to be associated with high PCSK9 levels, as has been not-

ed in the nephrotic syndrome. Knockout of PCSK9 in a mouse model of nephrotic syndrome was associated with improvement in dyslipidemia, which suggests a potential role of PCSK9 inhibitors in treating nephrotic syndrome-associated dyslipidemia (2).

Although PCSK9 inhibition has recently emerged as a promising therapy in reducing cardiovascular risk by aggressively targeting LDL cholesterol, the utility and efficacy of these agents in patients with CKD has yet to be defined. Pooled analysis of alirocumab efficacy data from eight ODYSSEY phase 3 clinical program trials in 4629 high-cardiovascular-risk patients whose levels of LDL cholesterol were inadequately controlled despite maximally tolerated statin with or without ezetimibe therapy showed that it was well tolerated and resulted in a 61% reduction of LDL cholesterol (3). The reduction in LDL cholesterol was maintained for the duration of therapy (up to 104 weeks). Also, there was a significant reduction in non-HDL cholesterol, apolipoprotein B, and lipoprotein A in contrast to statin therapy. These results were further supported by the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in subjects with Elevated Risk) trial, which evaluated the clinical efficacy and safety of evolocumab when added to standard statin therapy for patients with clinically evident atherosclerotic cardiovascular disease (4). LDL cholesterol levels were reduced by 59%, and the risk of major cardiovascular events was reduced by 15% in patients receiving evolocumab.

Data on the utility of PCSK9 inhibitors in patients with impaired kidney function are lacking, however. In 2018, Toth et al. (5) presented a subgroup analysis of pooled data from eight ODYSSEY phase 3 trials regarding the lipid-lowering effect and safety of alirocumab, particularly in patients with impaired kidney function (defined as baseline estimated GFR of 30–59 mL/min per 1.73 m<sup>2</sup>). It was found that alirocumab greatly lowered LDL cholesterol levels, along with apolipoprotein B and lipoprotein A, regardless of kidney function. Also, the reduction in LDL cholesterol did not vary with the level of proteinuria. It was generally well tolerated and did not affect renal function over time, irrespective of baseline renal function. However, patients with severe CKD (estimated GFR <30 mL/min per 1.73 m<sup>2</sup>) and ESRD were excluded from the initial trials and hence could not be studied.

Whether PCSK9 inhibitors should be prescribed to pa-

tients with kidney disease remains unclear. Although they provide an additional reduction of atherogenic lipids and thereby of cardiovascular risk in patients with relatively preserved kidney function, whether this benefit would be found in patients with advancing kidney disease or ESRD is uncertain. Whether this class of agent would be worthwhile will likely also depend on several factors, including the patient's underlying cardiovascular risk, the cost of the therapy, insurance coverage, and the patient's preference. It is important to keep in mind that the majority of trials excluded patients with progressive CKD, severe kidney impairment, and ESRD. Further research into the role of these and other novel agents in patients with kidney disease, while urgently needed, should be guided by remembering that cardiovascular risk in this population is determined by factors well beyond the basic mechanisms of atherosclerosis in the general population. ■

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# Improving the Involvement of People with Kidney Disease in Cardiovascular Trials

By Meaghan Allain and Zach Cahill

People with kidney disease are medically complex, and kidney disease may have an impact on the development of therapies to treat the many comorbidities affecting this population. Cardiovascular disease is a common and significant comorbidity among these patients, and individuals with kidney disease make up a sizeable proportion (30% to 60%) of patients with cardiovascular disease (1, 2). Yet, patients with kidney disease have often been excluded from cardiovascular clinical trials (1–4), thus limiting the evidence to guide treatment recommendations of cardiovascular disease for these patients.

The Kidney Health Initiative (KHI) is a public–private partnership between the American Society of Nephrology and the US Food and Drug Administration that focuses on catalyzing innovation and the development of safe and effective patient-centered therapies for people living with kidney diseases.

A KHI workgroup investigated the underrepresentation of people with kidney disease in cardiovascular clinical trials, with a particular focus on those with advanced kidney disease (stage 4 chronic kidney disease and kidney failure), and it identified potential solutions to addressing the barriers to their involvement.

“The project was executed by a diverse, international workgroup representing each stakeholder group involved in the issue,” said Charles Herzog, MD, KHI project co-chair. “We used a polling mechanism and a workshop to compile recommendations on the conduct of cardiovascular clinical trials from experts in clinical trials and people with cardiovascular disease and kidney disease, and their care partners.”

The workgroup discovered several challenges with involving people with advanced kidney disease in cardiovascular clinical trials, some of which may be more specific to cardiovascular clinical trials (e.g., lack of patient awareness of cardiovascular disease, need for additional work on appropriate cardiovascular endpoints), whereas others may apply more generally to clinical trials involving this population.

Given the safety risks and concerns that involving people with advanced kidney disease may potentially affect the efficacy results, a compelling business case must be made to justify their involvement, and the use of regulatory and financial incentives may help to mitigate risk. Additionally, the design and implementation of clinical trials can be adapted to address the safety and efficacy concerns about including this population.

More broadly, the workgroup highlighted the need for closer collaboration between nephrologists and cardiologists and the need for more systemic change within the nephrology community to prioritize the engagement and enrollment of patients with kidney disease into clinical trials. Despite the inherent advantages of the kidney disease population for clinical trials, such as a data-rich environment and regular contact with clinicians, nephrology lacks an “on-study” culture in which discussing clinical trial participation with people receiving dialysis or experiencing progression to kidney failure is the norm.

“Kidney care professionals need to lead the way in transforming the culture of kidney care into one that prioritizes clinical trials,” said Julie H. Ishida, MD, MAS, KHI project co-chair. “It will take leadership from nephrologists, collaboration with other specialties, and engagement with our patients to elevate the importance of clinical trials within our community.”

Today, the kidney community is experiencing a new

level of investment in novel therapies from pharmaceutical companies. Nephrologists need to take the lead in educating themselves and communicating the value of cardiovascular and other clinical trials to their patients and colleagues. There are many concrete actions the kidney community can take to empower nephrologists to lead in this area. Institutions, societies, and government can provide funding for trials, training in trial design and conduct, and educational resources about clinical trials for patients and care partners. Specifically, for cardiovascular trials, cross-specialty collaborations between cardiologists and nephrologists should be encouraged to improve patient enrollment and trial design and implementation. It will take all the players in the kidney community, including patient organizations, subspecialty societies, health-care organizations, research sponsors, and dialysis providers, working together to change the culture and create an environment that prioritizes clinical trials.

There are many contributors to the underrepresentation of people with advanced kidney disease in cardiovascular clinical trials, and building a compelling business case and adapting the design and conduct of clinical trials to facilitate their involvement are important. More fundamentally, cultivating an “on-study” mindset within the nephrology community and prioritizing the participation of both physicians and patients in clinical trials will help ensure that the appropriate treatment recommendations can be made for people with kidney disease for cardiovascular and other indications. ■

*Meaghan Allain is a senior project associate at the Kidney Health Initiative. Zach Cahill is a marketing and communications specialist at the Kidney Health Initiative, University of Rochester, Rochester, New York.*

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# Transplant Care Transformed in the Face of COVID-19

By Bridget M. Kuehn

As New York City hospitals braced for a potentially overwhelming surge of COVID-19 cases, Columbia University Medical Center nephrologist Sumit Mohan, MD, MPH, and his colleagues had to transform the way they provided kidney transplant care.

“We put a pause on nearly all kidney transplants,” said Mohan, an associate professor of epidemiology and medicine at Columbia University. All elective procedures were put on hold to free up space and ventilators for a surge of COVID-19 patients. For kidney transplant patients with living donors, they decided it was safer to postpone surgeries to prevent donors or immune-suppressed recipients from becoming infected with SARS-CoV-2 in hospitals with large numbers of COVID-19 patients. They concluded that the risks were also too high for most recipients of deceased donors’ kidneys, who in addition to being at risk of infection while immunosuppressed could also experience infection transmission from a donor organ, particularly given the severe shortage of tests for the virus in the early days of the pandemic.

“We inactivated the majority of patients on our kidney transplant list,” he said. Only a small subset of patients who

are highly sensitized and unable to accept 99% of donor organs were kept active in case a rare compatible organ became available.

“Our clinics were essentially emptied out except for a small set of urgent visits, Mohan said. “Whatever didn’t need an in-person visit became a telemedicine visit.”

## Drawing from experience

To care for kidney transplant patients who became infected with SARS-CoV-2, Mohan and colleagues drew on the experience of collaborators from Northern Italy. Their Italian colleagues were seeing large numbers for transplant recipients hospitalized, a high rate of acute kidney injury, and an influx of kidney failure.

“That conversation alerted us to the need to start preparing,” Mohan said.

Infectious disease specialists also helped by tapping their past experiences with respiratory infections and previous coronavirus outbreaks. Jay Fishman, MD, director of the Transplant Infectious Disease & Compromised Host Program at Massachusetts General Hospital, explained that transplant patients typically have more severe, prolonged symptoms of respiratory infections like pneumonia. Such patients also experienced more severe disease during outbreaks of the Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome, which are also caused by coronaviruses.

To help transplant patients fight COVID-19, Mohan and colleagues developed a standardized approach, the cornerstone of which included reducing patients’ immunosuppression (1). This is a common tactic in helping transplant patients fight infection, Fishman noted.

“We are always balancing immunosuppression against the risk of infection,” Fishman said. “That’s where we live.”

But COVID-19 can trigger an excessive immune response, and inflammation has added a challenge. Fishman noted that there is some question about whether immunosuppressive drugs may protect transplant patients against COVID-19–linked inflammation, but no one knows for sure. “We’ve taken a middle ground where we turned down immune suppression, but we don’t want rebound inflammation to occur,” he said.

With all our decision-making, “we were trying to be as systematic and data-driven as we could be in the chaos, and everyone understood that this was an all-hands-on-deck approach,” Fishman said.

Fishman said he hopes programs will be able to take what they have learned from COVID-19 to help improve transplant patient care even after the pandemic ends. As examples, he cited greater use of telehealth, reductions in unnecessary testing, more rapid testing therapies through collaborations across the country, and better use of electronic medical record data.

“All of these things are things that we’ve learned, it would be a shame not to build on them for our patients in the future,” Fishman said. ■

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# Findings

## Early resolution of AKI leads to better long-term outcomes

The first 72 hours after diagnosis of acute kidney injury (AKI) have a major impact on the long-term risk of kidney-specific outcomes, according to an analysis of prospective cohort data reported in *JAMA Network Open*.

The study included 1538 hospitalized patients from the prospective multicenter Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury (ASSESS-AKI) study: 769 patients with AKI and 769 without. Participants were enrolled 3 months after hospital discharge between 2009 and 2015, with follow-up to 2018. The two groups were matched for demographic characteristics, hospital, comorbidity, and preadmission estimated glomerular filtration rate (eGFR).

About 62% of patients had “resolving AKI,” defined as a decrease in serum creatinine concentration of  $\geq 0.3$  mg/dL or at least 25% from the peak value, within 72 hours after AKI diagnosis. The main outcome of interest was a composite of major adverse kidney events (MAKE): occurrence or progression of chronic kidney disease (CKD), long-term dialysis, or death of any cause.

The patients were 964 men and 574 women, mean age 64.6 years. At a median follow-up time of 4.7 years, the MAKE primary outcome occurred in 36% of patients: incidence rate 5.9 events per 100 patient-years in the non-AKI cohort, 11.9 events per 100 patient-years in those with resolving AKI, and 16.6 events per 100 patient-years in those with nonresolving AKI.

The adjusted hazard ratio (HR) for MAKE was 1.95 for patients with resolving AKI and 2.80 in those with nonresolving AKI, compared with the non-AKI group. The associations persisted after further analysis for KDIGO stage at 72 hours, shock, mechanical ventilation, and major surgery: HR 1.52 and 2.30, respectively.

Among patients with AKI, the risk of MAKE was 51% higher for those with non-resolving AKI: HR 2.40 for incident CKD and 1.58 for progressive CKD. The two AKI groups were at similar risk for dialysis and death. Associations between AKI recovery pattern and MAKE were independent of hospital length of stay, vasopressor initiation, and serum creatinine concentration at discharge.

The trajectory of kidney recovery after AKI provides useful information on the risk of poor short-term outcomes. The new results suggest that hospitalized patients with early resolution of AKI have better long-term outcomes.

Patients whose AKI doesn't resolve within the first 72 hours are at higher risk for MAKE, specifically incident and progressive CKD. Stratification by early recovery pattern may aid prognosis and targeting resources for follow-up and early detection of CKD [Bhatraju PK, et al. Association between early recovery of kidney function after acute kidney injury and long-term clinical outcomes. *JAMA Network Open* 2020; 3:e202682]. ■



## Center volume affects outcomes of pediatric kidney transplantation

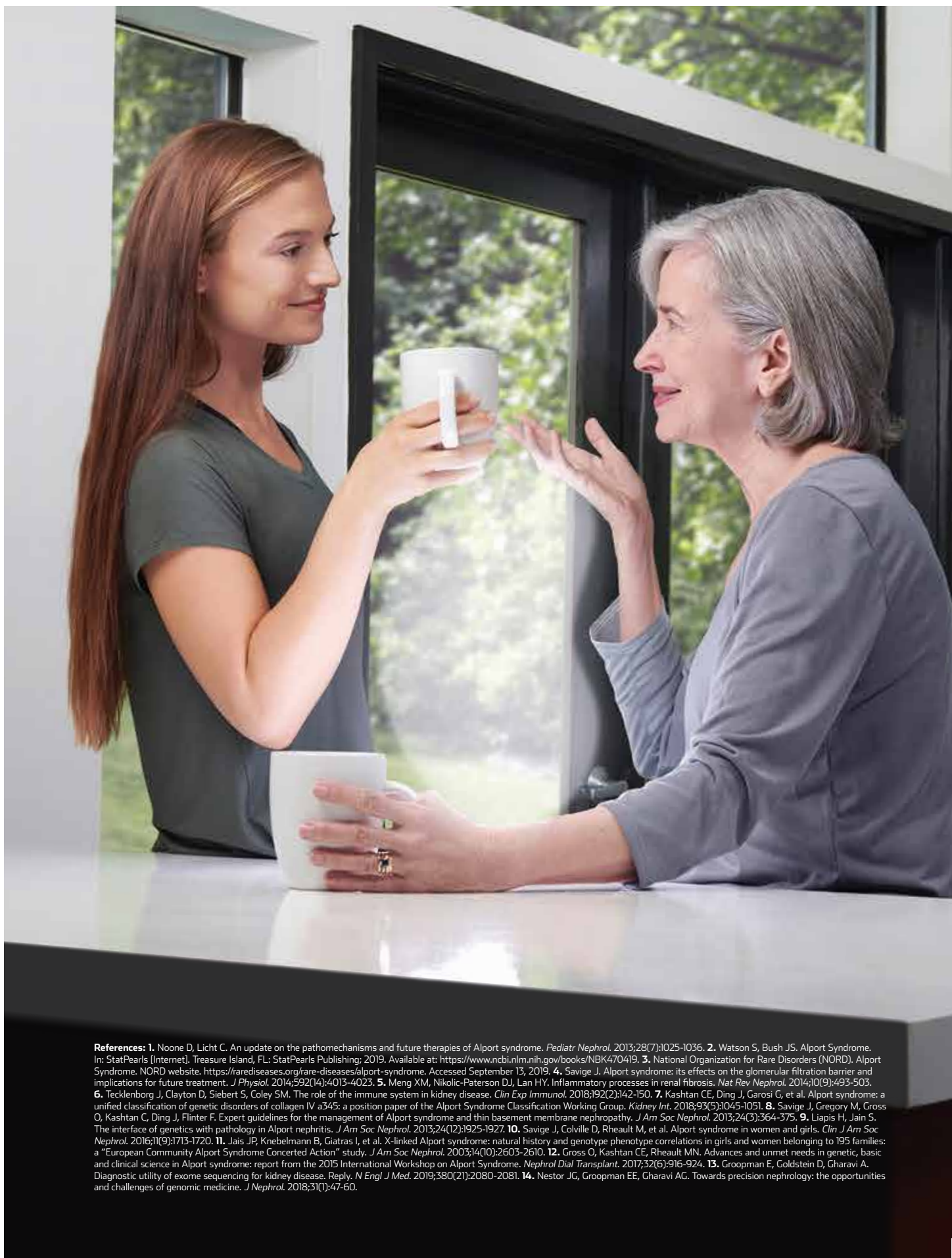
Higher-volume transplantation centers achieve better outcomes in children undergoing kidney transplantation, according to a study in *Kidney Medicine*.

The case-cohort study included data on 3762 kidney transplants in patients <18 years between 2010 and 2015, drawn from the Scientific Registry of Transplant

Recipients. Procedures were performed at 115 centers, which were classified as low-volume (fewer than four transplantations per year), intermediate-volume (four to eight per year), and high-volume (more than eight per year). The 3-year graft survival was compared among these volume groups, with adjustment for covariates.

The three groups of recipients were similar in terms of sex, age, ethnicity, kidney disease diagnosis, and kidney donor profile index score. The analysis included 2379 deceased-donor and 1383 living-donor transplantations.

The 3-year graft survival was 92.1% at centers performing a high volume of



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procedures, compared with 90.3% at intermediate-volume centers and 88.4% at low-volume centers. The number needed to harm was 27: for every 27 children treated at a low-volume versus high-volume center, there would be 1 additional patient with graft loss. The graft survival rates were better at centers in high-income versus low-income states, with no interaction between household income and center volume.

Center volume was related to the outcomes of living-donor transplantation: 3-year graft survival was 91.7% at low-volume and intermediate-volume centers

combined, compared with 95.3% at high-volume centers. There was no significant difference in outcomes of deceased-donor transplantation: about 89% in all three groups.

A recent study reported similar outcomes of adult kidney transplantation for centers performing differing volumes of transplantation procedures. Little is known about how center volume affects the outcomes of pediatric kidney transplantation, which constitute only about 2% of procedures nationwide.

The new study finds lower 3-year graft survival in children undergoing kidney

transplantation at lower-volume centers. The effect of volume is most marked for living-donor kidney transplantations. The 1-month survival is similar across volume groups. This finding “argues against surgical factors being a key factor and suggests that limited experience may compromise the optimal handling of immunosuppression and prevention of infection accounting for the differences in 3-year graft survival,” the researchers write [Contento MN, et al. Center volume and kidney transplant outcomes in pediatric patients. *Kidney Med* doi: 10.1016/j.xkme.2020.01.008]. ■

## C1-inhibitor may help prevent contrast-induced nephropathy

Given before coronary angiography in high-risk patients, recombinant human C1-esterase-inhibitor (rhC1INH) reduces biomarkers for contrast-induced kidney injury, reports a trial in *JACC: Cardiovascular Interventions*.

The Prophylactic RhC1-inhibitor to Prevent Contrast-induced Nephropathy (PROTECT) trial included 77 high-risk patients scheduled for elective coronary angiography. All had an eGFR of  $\leq 50$  mL/min per  $1.73 \text{ m}^2$  plus one additional risk factor (diabetes, age  $\geq 75$ , anemia, congestive heart failure, or history of pulmonary edema). The patients were 54 men and 23 women, mean age 77 years and mean eGFR 40 mL/min per  $1.73 \text{ m}^2$ .

Patients were randomly assigned to treatment with rhC1INH 50 IU/kg or placebo before and 1 hour after coronary angiography. The main efficacy outcome was peak change in neutrophil gelatinase-associated lipocalin (NGAL), a biomarker of kidney injury. Secondary outcomes included contrast-induced nephropathy (CIN), based on serum creatinine increase of at least 25% or 0.5 mg/dL, and a  $\geq 10\%$  increase in cystatin C.

On per-protocol analysis, rhC1INH was associated with a lower peak change in NGAL: 4.7 ng/mL versus 22.5 ng/mL. However, a modified intention-to-treat analysis found no significant difference: 7.2 ng/mL versus 22.5 ng/mL, respectively.

On a post hoc analysis of patients undergoing percutaneous coronary intervention, the peak change in NGAL was sharply lower in the rhC1INH group: median 1.8 ng/mL versus 26.2 ng/mL.

Sixteen percent of patients receiving rhC1INH had a cystatin C increase of  $\geq 10\%$  within 24 hours, compared with 33% of the placebo group. The CIN rate was similar between groups: 10.5% and 5.6%, respectively. Adverse events were comparable as well.

New approaches are needed to prevent contrast-associated kidney injury in high-risk patients. rhC1INH, which is approved for the treatment of hereditary angioedema, has been shown to reduce renal ischemia/reperfusion injury in animal models.

This proof-of-concept study reports reductions in NGAL and cystatin C in high-risk patients receiving rhC1INH before elective coronary angiography. The protective effect appears larger in patients undergoing percutaneous coronary interventions.

The authors call for larger clinical trials of rhC1INH for this indication, addressing CIN rate and other meaningful clinical outcomes [Panagiotou A, et al. A randomized trial of recombinant human C1-esterase-inhibitor in the prevention of contrast-induced kidney injury. *JACC: Cardiovasc Interv* 2020; 13:833–842]. ■

# It's time for kidney talk

When you see unexplained signs of kidney disease, think **Alport syndrome**. It can filter through a family.

## Incurable disease

- Alport syndrome (AS) is a **permanent, hereditary condition** responsible for a genetically defective glomerular basement membrane, causing chronic kidney inflammation, tissue fibrosis, and kidney failure<sup>1-6</sup>
- Across the entire range of AS genotypes, **patients are at risk of progressing towards end-stage kidney disease (ESKD)**<sup>3,7,8</sup>

## Hidden signs

- Patients often go undiagnosed**, as the clinical presentation of AS is highly variable and family history may be unavailable<sup>3,9-11</sup>
- Persistent, microscopic hematuria is the cardinal sign of AS** and should prompt immediate diagnostic investigation—particularly when combined with any family history of chronic kidney disease<sup>8,11,12</sup>

## Early action

- Expert guidelines published in the *Journal of the American Society of Nephrology* now **recommend genetic testing as the gold standard for diagnosing Alport syndrome**<sup>8</sup>
- Early AS detection via genetic diagnosis, and its ability to guide a patient's treatment decisions, demonstrates the **powerful impact of precision medicine in nephrology**<sup>12-14</sup>

Reata and Invitae have collaborated to offer no-charge genetic testing for rare chronic kidney disease diagnosis and greater clinical insights. For more information regarding the KIDNEYCODE program or to order a test, please visit [www.invitae.com/chronic-kidney-disease](http://www.invitae.com/chronic-kidney-disease) or contact Invitae client services at [clientservices@invitae.com](mailto:clientservices@invitae.com) or 800-436-3037.

**Abnormal kidney function can have a strong family connection—  
Alport syndrome**

Learn more about Alport syndrome at  
[ReataPharma.com](http://ReataPharma.com).



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## Fellows Corner

# Uncertainty Amid COVID-19 Pandemic An International Medical Graduate's Stance

By Sai Sudha Mannemuddhu



Sai Sudha Mannemuddhu

International medical graduates (IMGs) play an important role in the US healthcare delivery system. About a quarter of the 800,000 practicing physicians are IMGs, and 41% of practicing IMGs are in primary care disciplines (1). These physicians play a vital role in the care of vulnerable populations in the underserved areas of both urban and rural settings. In a survey conducted in pediatrics, international IMGs are more likely to work in underserved areas than are American medical school graduates (2).

About 18% of graduating pediatric residents are IMGs, and about 25% of fellows are IMGs (3). About 40% and 42% of internal medicine residents and fellows, respectively, are IMGs, and at least two-thirds of them are dependent on visas (4). The most common type of visa used by IMGs to participate in US medical programs is the J1 visa. Other types of visas are H1B and J2.

Limiting the number of working personnel in many government offices, including the US Citizenship and Immigration Services (USCIS), will affect the processing of visas for graduating physicians, residents, and fellows, po-

tentially leaving them unemployed for a few months after graduation, which is usually June 30, 2020.

### What does this mean for healthcare?

Inasmuch as approximately 20% to 30% of graduating physicians are dependent on visas, and most trainees with J1 visas will take jobs in underserved areas, delays in visa processing can have a significant impact on the healthcare delivery system. With graduating fellows and residents being unemployed for the first few months of the academic year, starting in July 2020, the number of physicians will decrease, particularly in underserved areas with physician shortages. The front line physicians during the COVID-19 pandemic are internists, critical care physicians, nephrologists, and primary care physicians, to mention a few, and the great majority of IMGs belong to these physician groups.

With fewer physicians available to practice, patients' waiting times may increase, and that can jeopardize their health. Fewer physicians could also mean patients must travel longer distances than usual to seek medical care, which is an additional burden. The number of people visiting emergency rooms will increase further as patients may try to wait out worrisome medical problems. Overburdened emergency rooms can result in more waste of resources and compromised medical care. Also, emergency rooms will increase the exposure of patients and staff to contagious disease, creating a vicious cycle. Overloading the healthcare system will lead to stress and burnout and can potentially add to this cycle.

### What does this mean for physicians?

One of my friends said, "Perhaps this delay is a month or two. The problem is no pay and no driver's license during those months, but other than that we should be OK." Is it that simple, or are we falsely reassuring ourselves to get our lives moving?

Trainees who complete their training will have a grace period of 30 days before traveling to depart the country, during which time the person is not using any visa but is under the jurisdiction of the USCIS (6). Also, it is legal to stay in the United States as long as one has applied for a valid visa and it has not been rejected. If a trainee is scheduled for a board examination, the visa can be extended for up to 6 months (7).

Even though one can stay in the United States legally, one is not allowed to work, which translates to no pay. Most IMGs do not have family in the United States, and they cannot go home because, when one leaves the United States when a visa is in process, all the submitted paperwork is nullified, and one has to start everything from scratch amid the closure of many embassies in their respective foreign countries. Imagine the time and expense that go into this process, particularly when one is unemployed!

What about the mental and physical well-being of these physicians, who have just served the country on the front lines during this pandemic? Some may even be recovering from COVID-19. Additionally, working for long hours in close proximity to sick patients—and the inability to completely prevent negative patient outcomes—can cause a significant emotional drain. And what about physician burnout? Not having a family close

by and the inability to visit loved ones can only worsen these physicians' physical and mental health (Figure 1).

Moreover, when visas are finally approved, these physicians now have the pressure of adjusting to new job environments. This, again, is a great stressor even in the best of circumstances. If children are added to this equation (which applies to about 40% of pediatric IMGs) (8), it is utterly incomprehensible.

Not the least, our inability to help our patients when they are in a dire situation can cause substantial guilt.

### Is there a possible solution?

There is no standard solution. But because all these issues stem from the visa/change of status situation, focusing on this one issue could help fix all the associated problems. Inasmuch as premium processing (which usually is done within 15 days) is on hold at this time, and regular visa processing requires at least 3 to 12 months and can be further delayed amid the pandemic, solving this problem could potentially mitigate all the issues faced by both patients and physicians.

The USCIS could consider allowing expedited processing for physician visas. Nonprofit organizations like the Education Commission for Foreign Medical Graduates and the Exchange Visitor Sponsorship Program can petition the USCIS for expedited processing. Associations of immigration lawyers who work closely with physicians can help authorities understand the need for physicians during this dire situation. Hospital administrations can meet with senators and members of Congress and seek their help. We physicians can write to or speak with government representatives as well.

With these few thoughts, I would like to conclude by saying, we are all in this together—and stay safe, dear friends.

### Acknowledgment

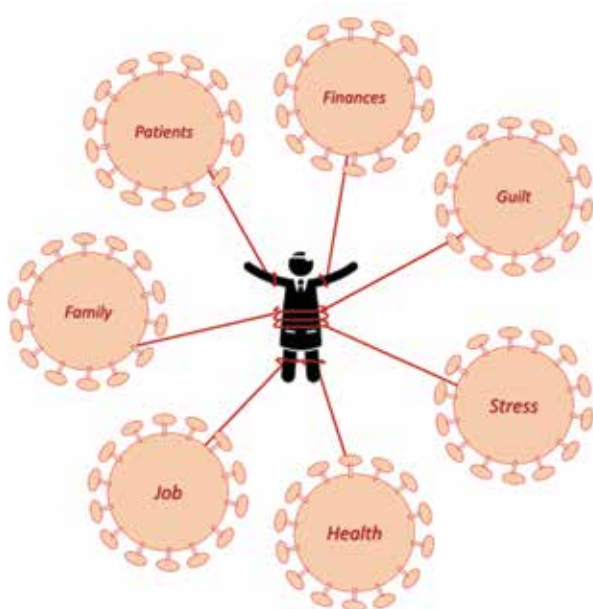
The author thanks Dipankar Gupta, MD, for reviewing this article. ■

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**Figure 1. Compromised physician well-being amid stressors due to COVID-19**





# Being a Fellow in the Time of COVID-19

By Kartik Kalra



Kartik Kalra

In mid-January 2020 I first heard about COVID-19. At first, it came across as yet another respiratory viral disease that had moderately higher infectivity compared with previous viruses. I never imagined that it was just the beginning of what would become a pandemic and that later case numbers would be staggering and overwhelming. COVID-19 has taken a toll not only on patients but also on healthcare systems, their workers, and the economy.

Sooner than I could comprehend the full extent of the damage, I found myself engulfed in the midst of this pandemic. It now feels like *Game of Thrones*, where the great battle has begun. I echo the sentiments of series character John Snow about getting all the houses together and asking for help irrespective of differences, trying to highlight his point that “the only war that matters now is the war for survival.” The major difference here is that we are fighting an invisible enemy. The only weapon we have is hope and a belief that despite everything, humanity will prevail.

The world is watching and looks up to us as healthcare workers during this pandemic, and I believe this is a time when we as a community can grow stronger. Years of medical school, residency, and fellowship have cultivated our art of listening and delivering news to our patients, acting in their best interest, and always advocating for their wishes.

As a member of the medical fraternity, I am humbled to see that despite the stress and anxiety, healthcare professionals are valuing each other as never before. They are pitching in and helping out in any way possible. A hospitalist friend in New York City told me his team includes himself, an orthopedic attending, and two psychiatric residents, each of whom manages the treatment of COVID-19 patients. Never before in medicine have I seen such unification of disparate fields and such abandonment of existing hierarchies.

What can we do as nephrologists? We need to remind our patients and families to have hope and stay positive, and we need to educate and update them as new information becomes available. We can help patients broaden their understanding of COVID-19 and be extra considerate in addressing the smallest of their doubts. We can discuss ways to minimize contact. And we need to keep in mind that

our dialysis nurses and technicians do not have the luxury of minimizing contact and are equally involved in this war, if not more so. The least we can do is to be overwhelmingly appreciative of their work.

## My apprehensions as a fellow

Fear grips me every time I examine a patient being admitted with COVID-19-like symptoms—fear that I will infect my patients, family, and colleagues. But have I not already seen infected patients? Have I not felt this fear every time I have entered a room with precautions? Not necessarily. There might be a moment of reflection in these cases, but it soon passes.

As healthcare advocates, we often are so consumed by the infections and pathologic conditions we see that we often forget the emotional baggage our job carries. We become immune to, or many times forget, that we are in the middle of a pandemic, and that some of us may not survive. We try to maintain our composure as we see the growing number of cases, as we talk to another friend or colleague who is currently infected or recovering from the illness.

## My worries

I worry about my family in India, where the number of cases is increasing by the day.

I wonder if I will be able to start my new job on time, given the visa situation during the pandemic. I am on a work visa, and the US Citizenship and Immigration Services currently has suspended all visa renewals and premium processing, leaving many of us in an immigration limbo. Like many other physicians, I want to offer my services but cannot because of visa restrictions.

The COVID-19 situation here in Pittsburgh is still under control and flattening out, if you go by the numbers, but it is just a silent wait before the storm. A daily flurry of emails from hospital administration and staff update us about changing policies. Our department updates us about any new innovations or changes in guidelines. We try to review the latest scientific literature, and thanks to #FOAMED and academia using social media, we have updates from experts. Everything progresses quickly, leaving us hardly enough time to catch up.

The emotional and psychologic toll on healthcare workers is worsened by the lack of personal protective equipment (PPE) and a constant fear of infecting loved ones. I fear that this will eventually lead to burnout and mental breakdown. The idea that doctors are indispensable and are equipped to face any circumstance is complicated by these fears. Our community at large is fighting for PPE so that we

can minimize the risk to our lives and save other lives down the road. If this is a war, PPE is the armor we need.

## Has our practice changed since the beginning of the outbreak?

The epidemic has had a large impact on clinical practice. Many elective procedures have been canceled to limit patient exposure. Telemedicine and video visits have replaced office visits to a great extent (Figure 1).

The Centers for Medicare & Medicaid Services, which decides on reimbursement and billing strategies, as of March 6, 2020, reimburses for office and hospital telehealth visits. Payment for telephone visits now matches payments for similar office and outpatient visits.

Overall, I believe this is a major change to our clinical practice, and clinicians are becoming more comfortable with the idea of video and telephone visits. So far, I have observed better patient satisfaction and a lower no-show rate, likely attributable to lower risk of infection, travel-related issues, and scheduling of multiple other appointments. Various platforms compliant with the Health Insurance Portability and Accountability Act are currently in use by each institution (e.g., Zoom, Skype for business, Microsoft Teams). At our institution, Vydo software is integrated with our electronic health records. The overall idea is to expand the use of this technology to maximize patient care and minimize patient risk, thereby limiting the community spread of COVID-19.

## How has the fellowship program adapted?

A standard 2-year nephrology training program can be divided into core consult rotations (e.g., critical care nephrology, transplantation, outpatient dialysis); electives (e.g., glomerulonephritis, onconeurology, specialized clinics); and outpatient experience. Different programs divide these rotations according to their fellowship structures. Most of the core rotations at my program are in the first year, leaving the second year for electives and scholarly activities. Keeping social distancing in mind, our program leadership decided to cancel all in-person conferences and quickly transition to the model of virtual learning through Microsoft Teams. Initially we had a few hiccups, as one would have while adapting to a new platform. Currently all our conferences, journal clubs, resident lectures, and weekly updates on COVID-19 are held through Teams. It is interesting that the Glomerular Disease Study and Trial Consortium has had the same model for more than 2 years and is at-

Continued on page 24 ➤

Figure 1. Summary of Medicare telemedicine services

| Type of Service                   | What is the service?                                                                                                                                                                                                                           | HCPCS/CPT CODE                                                                                                                                                                                                                                                                                                                                          | Patient Relationship with Provider                                                                                                                                                                                                            |
|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>MEDICARE TELEHEALTH VISITS</b> | A visit with a provider that uses telecommunication systems between a provider and a patient.                                                                                                                                                  | Common Telehealth services include:<br><ul style="list-style-type: none"> <li>99201-99215 (Office or other outpatient visits)</li> <li>G0425-G0427 (Telehealth consultations, emergency department or initial inpatient)</li> <li>G0406-G0408 (Follow-up inpatient telehealth consultations furnished to beneficiaries in hospitals or SNFs)</li> </ul> | For new* or established patients<br><br>*To the extent the 1135 waiver requires an established relationship, HHS will not conduct audits to ensure such a prior relationship existed for claims submitted during this public health emergency |
| <b>VIRTUAL CHECK-IN</b>           | A brief (5-10 minutes) check in with your practitioner via telephone or other telecommunications device whether an office or other service is needed. A remote evaluation of recorded video and/or images submitted by an established patient. | <ul style="list-style-type: none"> <li>HCPCS code G2012</li> <li>HCPCS code G2010</li> </ul>                                                                                                                                                                                                                                                            | For established patients                                                                                                                                                                                                                      |
| <b>E-VISITS</b>                   | A communication between a patient and their provider through an online patient portal.                                                                                                                                                         | <ul style="list-style-type: none"> <li>99421</li> <li>99422</li> <li>99423</li> <li>G2061</li> <li>G2062</li> <li>G2063</li> </ul>                                                                                                                                                                                                                      | For established patients                                                                                                                                                                                                                      |

## Being a Fellow

Continued from page 23

tended by trainees and physicians the world over. (I wonder whether we should have adapted to this learning model earlier.) Any non-COVID-19 discussion is healthy and keeps the mind diverted, restoring some normalcy.

At present, during the case surge in Pittsburgh, we have not been deployed to cover COVID-19 patients or rotate in the critical care unit—although if cases start to peak, fellows might be redirected to cover COVID-19 services. Again, this is an unprecedented situation. Desperate situations require desperate measures. Patient care cannot be compromised.

### Coping mechanisms

As a result of social isolation and the need to “shelter in place,” many of us are anxious. We as healthcare workers are particularly vulnerable to stress and anxiety as we strive to strike a balance between personal and professional well-being. Fortunately, our program at Pittsburgh has aggressively adapted to this challenging situation by identifying trainees involved with electives and nonessential services and excusing them from coming to the hospital unless they are needed. I personally recommend Headspace; virtual happy hours with colleagues, other fellows, and friends; and a daily exercise regimen to help cope. We need to be eminently prudent about the well-being of healthcare workers in the fight against COVID-19 [ <https://www.ama-assn.org/practice-management/physician-health/covid-19-front-line-mount-sinai-keeps-physician-well-being>].

### Living history

The direction of this pandemic is not driven by political whims and fancies. We don’t decide the course; the virus does, as National Institute of Allergy and Infectious Diseases Director Anthony Fauci reminds us.

Writing in a blog post for NephronPower, New York nephrologist Kenar Jhaveri, MD, said, “Not only is the virus infecting people, it’s infecting the hospital itself. It’s pushing out everything else.”

We are living history. Nothing has prepared us for this. Soak it in. I hope that 40 years from now we will be telling our grandchildren how we served on the front lines of the great 2020 pandemic. We may never again have the opportunity to be involved in something more meaningful. ■

*Kartik Kalra, MD, is a nephrology fellow at the University of Pittsburgh Medical Center.*

# Transplant Centers Adjust Policies, Take Precautions during COVID-19

By Karen Blum

As COVID-19 started to take hold in countries like China and Italy, Marian Michaels, MD, MPH, thought the transplant community in the United States and Canada would benefit from having information about the then-rising epidemic so they could establish solid plans for their patients and programs. She had no idea how prescient that decision would be.

Michaels, a pediatric infectious diseases physician at UPMC Children’s Hospital of Pittsburgh, gathered fellow infectious disease transplant experts to publish a framework for keeping patients and hospital staffs safe during an outbreak of COVID-19 (1). Michaels noted that individual transplant centers may be affected by COVID-19 differently depending on the amount of virus in their institutions and their patient populations, so each must regularly update protocols regarding how they can continue to perform transplants safely and when they may need to slow things down.

- Targeted, screening of patients and visitors, and for OPOs, of potential donors.
- Plans for placement and evaluation of recipients with risk factors for the pathogen when they are sick and require evaluation.
- Backup plans for recipients requiring evaluation for other reasons if a transplant center is temporarily closed.
- Consideration for candidates to be listed at alternative centers for transplant if an epidemic is geographically confined.
- The ability to communicate with transplant recipients and potential living donors to keep them apprised of updated information and recommendations.

What has changed with COVID-19 are additional recommendations for transplant patients and their family members to protect themselves by wearing masks, practicing

good hand hygiene, and physical distancing, Michaels said. Living donors also should self-quarantine before the donation so they are not exposing themselves prior to surgery.

Uday Nori, MD, an associate professor of medicine and program director of the nephrology fellowship program at The Ohio State University Wexner Medical Center, agreed with Michaels that transplant centers are making decisions based on their own unique needs at this time. While Nori’s medical center canceled elective procedures including living donor kidney transplants, for now, the program has actively been performing about two deceased donor kidney transplants per day.

“Other centers have been passing up organs so we started getting many more imports,” he said. “I feel really good about it. We don’t want to waste any donor organs because they’re precious ... and there’s only a finite amount of time before they are discarded.”

The program did add some extra precautions, Nori said. Every donor and recipient is checked for COVID-19 through testing from the National Kidney Registry. The medical center’s transplant unit is maintaining its policies of restricting visits from children, as well as deliveries of fresh fruit or flowers. Nurses who work in the transplant unit have not participated in a float pool to provide backup help for other units that may have COVID-positive patients.

Additionally, physicians modified the immunosuppression protocol so those at high risk for COVID would not be as heavily immunosuppressed, and they are conducting more post-transplant follow-up visits by phone or video.

“I’m very optimistic,” Michaels said. “I know this has been very hard on all of us, and it’s been difficult watching our friends and patients hospitalized, but I’ve been amazed at the resiliency and also the ability of people to work together.”

Nori said the volume of information pouring out about COVID-19 now is almost overwhelming. He estimates he spends about two hours a day sifting through updated information about the pandemic, including emails he receives through an American Society of Transplantation listserv called Outstanding Questions in Transplantation Research.

“It’s one of the most valuable things I’ve seen for COVID, because people are sharing even unpublished manuscripts because they don’t want people to be hamstrung by not having information on a daily basis,” said Nori, a member of the *Kidney News* editorial board.

“When COVID-19 hit the US, I don’t feel we had as many protocols in place for dealing with this as we have now,” Michaels said. “Being able to say what your resources and capacity are and having educational tools ready to get to patients is going to put us ahead of the game more [in the future] than what we had for this pandemic.” ■

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**Being able to say what your resources and capacity are and having educational tools ready to get to patients is going to put us ahead of the game more [in the future] than what we had for this pandemic.**

“The emergence of COVID-19 is not the first time the transplant community has had to contend with emerging viruses, nor will it be our last,” Michaels and colleagues write in the paper. “Consequently, we should learn from past experiences with novel viruses and put safeguards in place for transplant centers and OPOs [organ procurement organizations] to protect transplant recipients and healthcare workers ... and to mitigate the impact of this epidemic on transplant outcomes.”

Based on lessons learned from previous outbreaks of related viruses, such as the 2002 outbreak of SARS-CoV and the 2012 outbreak of MERS-CoV, Michaels said transplant programs should have the following protocols in place:

ing good hand hygiene, and physical distancing, Michaels said. Living donors also should self-quarantine before the donation so they are not exposing themselves prior to surgery.

Uday Nori, MD, an associate professor of medicine and program director of the nephrology fellowship program at The Ohio State University Wexner Medical Center, agreed with Michaels that transplant centers are making decisions based on their own unique needs at this time. While Nori’s medical center canceled elective procedures including living donor kidney transplants, for now, the program has actively been performing about two deceased donor kidney transplants per day.

“Other centers have been passing up organs so we start-





“As a renal pathologist, I love how what I do not only helps my patients, but also other physicians. I am grateful to be key in guiding the treatment of kidney disease by the interpretation and assessment of kidney biopsies. As I continue to work with my nephrology colleagues on new developments in kidney disease classification, I am also proud to play a role in the education of medical students, residents and fellows.

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# METABOLIC ACIDOSIS IN CHRONIC KIDNEY DISEASE (CKD) IS COMMON AND HARMFUL<sup>1-7</sup>

## ▼ Chronic metabolic acidosis damages kidney, bone, and muscle<sup>1-4</sup>

- Its pathophysiology is associated with loss of bone mineral density<sup>8-10</sup>
- It contributes to muscle wasting in CKD as a result of increased muscle catabolism<sup>8,10</sup>
- It is both a complication of chronic kidney disease and a cause of its progression<sup>4,5,8,10,11</sup>

▼ Learn more at **[MetabolicAcidosisInsights.com](https://MetabolicAcidosisInsights.com)**

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