The rising tide of kidney disease

Rates of end-stage kidney disease have risen 35 per cent in Canada since 2008, so that more than 40,000 people nationwide are on dialysis or have received a kidney transplant. In Nova Scotia, approximately 1,500 people are in this situation.

“Once kidney function is so seriously compromised, dialysis, transplant and non-dialysis conservative care are the available treatment options,” notes Dr. Karthik Tennankore, director of research in the Division of Nephrology at Nova Scotia Health Authority and Dalhousie University. “Our goal is to improve health and quality-of-life outcomes for patients with kidney disease and to achieve the best possible outcomes when dialysis or transplantation become necessary.”

As much as 60 per cent of all kidney disease is related to diabetes—although high blood pressure and hardening of the arteries are also key risk factors. Nova Scotia faces a heavy burden of kidney disease, due to its high rates of diabetes and heart disease.

Half a dozen lead investigators in the Division of Nephrology are exploring how to improve health care and outcomes for patients with kidney disease, with help from NSHA staff members, residents and medical students. The researchers have secured funding from local and national agencies, including the Kidney Foundation of Canada and Canadian Institutes of Health Research (CIHR) for a wide range of studies.

The added challenge of frailty

Frailty—the accumulation of health deficits to increasing levels of vulnerability—is one of the key challenges researchers in the Division of Nephrology are working to address. Many patients with kidney disease are frail, especially since kidney disease can lead to inflammation, high blood pressure, low appetite, bone and muscle loss and other issues that increase frailty.

“We need to know how a person’s degree of frailty affects their health trajectory when they have kidney disease, especially while they are on dialysis and/or waiting for a kidney transplant,” notes Dr. Tennankore. “Kidneys are a scarce resource and transplantation should be reserved for those with a high probability of surviving beyond wait times.”

Dr. Tennankore is the principal investigator of a five-year CIHR-funded study involving seven centres and a target of 1200 patients in an effort to understand how frailty affects patients on the waitlist for a kidney transplant. “We need to know how the severity of frailty and a person’s suitability for a kidney transplant change over time,” he says. “Frailty could be a contraindication for transplant, or it could be a reason to prioritize patients.”
Frailty and dialysis

A patient’s degree of frailty has an enormous impact on how well they do on dialysis, as Dr. Karthik Tennankore discovered a few years ago with help from an NSHA Research Fund grant. He and his colleagues used the Clinical Frailty Scale (developed at NSHA and Dalhousie) to measure dialysis patients’ frailty, then compared these results to the patients’ health outcomes over time.

“We found that every one-point increase on the Clinical Frailty Scale increased a dialysis patient’s risk of death by 22 per cent, regardless of age,” Dr. Tennankore says. “This was a huge finding that really launched this research area for us.”

“We knew we needed a way for paramedics to accurately predict a patient’s need for urgent dialysis, so patients who need it get to Halifax as quickly as possible,” says Dr. Tennankore. “We’ve developed a risk-prediction model and have more funding from NSHA to test its accuracy. Ultimately we want to develop a quick and easy tool for paramedics to use.”

Emergency landing—Studies in the Division of Nephrology have found that half of all dialysis patients require one or more transports to emergency soon after starting dialysis, and these patients use ambulance services 10 to 30 times more than the general population. Some require urgent dialysis, involving close observation and a heart monitor. However, the researchers found that more than 30 per cent of patients who needed urgent dialysis were transported to facilities that lacked this capability. This sparked a whole new line of research.

Hospitalization risk—On average, dialysis patients are admitted to the hospital more than once a year; more than 30 per cent of these admissions are followed by another admission in the next 30 days. Preliminary work at NSHA suggests that 90 per cent of the most severely frail patients are hospitalized to start dialysis or experience one or more hospitalizations after they start.

Researchers in the Division of Nephrology want to make sure that patients with kidney disease understand how their degree of frailty—and the intervention of dialysis—will affect their wellbeing over time.

“Dialysis can be a lifesaving bridge to transplant and restore quality of life for many patients,” notes Dr. Tennankore. “Frail patients, however, may face significant challenges should they choose dialysis. Research is helping us improve how we monitor frailty and predict the risk of negative outcomes, so patients can make more well-informed decisions about their care.”
At any given time, the Division of Nephrology is involved in half a dozen clinical trials to test and/or validate new approaches to managing the many issues that arise with dialysis and kidney disease. These include:

Heart problems—NSHA nephrology researchers are involved in three international studies of heart health in dialysis, designed to improve management of atrial fibrillation (an arrhythmia), heart failure, heart attack and other major adverse cardiac-related events that can occur in dialysis patients.

Patient experience—Ten to 15 per cent of dialysis patients in Nova Scotia have been taught how to administer their treatments in the comfort of their own homes, saving them hours of travel to and from hospital. Researchers in the Division of Nephrology are leaders in learning how best to support home dialysis patients through electronic tools that allow patients to track vital information and stay virtually connected to their care providers. They received a QEII Foundation TRIC (Translating Research Into Care) grant for one pilot study and are now co-investigators on a multi-site CIHR-funded study of an e-health intervention for home dialysis patients.

Catheter and circuit function—Patients on dialysis require a catheter to be inserted into either a major vein (hemodialysis) or the abdomen (peritoneal dialysis). NSHA researchers, including pharmacist Dr. Jo-Anne Wilson, are involved in national clinical trials testing various protocols designed to optimize hemodialysis catheter function. It is also essential to prevent blood clots from forming in the tubing and machinery that allows the blood to be filtered outside the body in hemodialysis. NSHA researchers are taking part in an early-phase study testing an alternative to the blood thinner heparin, to see if it can reduce bleeding risk while still protecting against clots.

Anemia—Clinical trials comparing oral medications to intravenous treatments aimed at preventing or reducing anemia in kidney patients are underway at NSHA.

Itching—Many dialysis patients suffer from intense itching of the skin that no amount of scratching can relieve. NSHA researchers are planning to enroll patients in an international study of an intravenous agent to combat dialysis-associated itch.
Making the right match for long-term transplant success

While the number of patients waiting for a kidney transplant has risen by 400 per cent over the past 25 years, the number of kidney donors has risen by only four per cent. Unless they have a live donor, Atlantic Canadians in need of a new kidney are waiting more than four years for a suitable organ to become available for transplant. And, many patients require a second and even third kidney transplant over the course of their life, adding more pressure to the limited supply of organs.

“If we optimize donor-recipient matching, we can maximize the longevity of the transplant and minimize the need for repeat transplants.”

Beyond increasing the pool of living donors, optimizing the match between kidney donors and recipients is key. “If we optimize donor-recipient matching, we can maximize the longevity of the transplant and minimize the need for repeat transplants,” says Dr. Amanda Vinson, an NSHA nephrologist and leading researcher in donor-recipient pairing.

“This way, we can make the best use of a precious resource.”

Matching for sex—A kidney from a female donor may be too small for a male recipient—but there’s more to sex-matching kidneys than size. Dr. Vinson has received more than $70,000 from the NSHA Research Fund and the University Internal Medicine Research Fund to learn why women appear to have worse outcomes when they receive transplant kidneys from male rather than female donors.

“We’re not entirely sure why this happens, but the theory is that women may make antibodies to the Y chromosome on male kidneys when they are pregnant with a boy,” Dr. Vinson explains. “This could lead to higher rates of rejection when women with pre-transplant sons receive kidneys from male donors. We want to learn more about the mechanisms and how we might prevent this organ rejection.”

Matching for size—Dr. Vinson has captured international attention for her work on the importance of matching donors and recipients by size. “If a sex-mismatched donor is 30 kilograms smaller than the recipient, the risk of graft failure is about the same as if the donor had diabetes, even if the transplant kidney is healthy,” notes Dr. Vinson. “In other words, the donor-recipient mismatch increases the risk of graft failure by 50 per cent. If the donor and recipient are mismatched by size alone, the risk of rejection is increased by 20 per cent.”
As the need for healthy kidneys rises, researchers are gathering evidence to show that people who donate a kidney—while they are still alive—continue to be healthy.

“As long as live kidney donors are chosen carefully, donating a kidney is safe,” says Dr. Christine Dipchand, a senior staff nephrologist at NSHA. “It’s a pool of potential donors we can increase to improve outcomes for our patients.”

Dr. Dipchand is part of an international research network following the long-term health outcomes of live kidney donors since 2004.

“It’s the largest effort ever undertaken to understand how these incredibly generous people are doing, far beyond the usual follow-up horizon of two to five years,” Dr. Dipchand says. “We’re seeing very good long-term outcomes for donors.”

Worldwide, about 40 per cent of the kidneys used for transplant come from live donors—in Nova Scotia, these rates are lower, from 10 to 20 per cent. It is not necessary to be related to the recipient, only to be a compatible match. This is determined through blood tests and genetic tissue-typing.

“A lot of people are giving kidneys to strangers,” notes Dr. Dipchand. “We assess their health before the procedure to ensure they are in good condition and follow them closely for years afterwards.”

Matching for age—As Dr. Vinson notes, it is not necessary or even desirable for a 70-year-old to receive a 20-year-old kidney. “An older patient can safely receive an older kidney,” she says. “Age-matching donors and recipients allows us to reserve younger organs for younger patients, who may get more years out of their kidney transplant. This reduces the need for repeat transplants down the road. Conversely, if we give an older kidney to a young patient, they are more likely to outlive their graft and require another transplant.”

Dr. Vinson and her colleagues are looking into other ways to expand the donor pool by opening up the donor criteria.

One study, for example, examined the feasibility of transplanting hepatitis-C-infected kidneys into donors also infected with hepatitis C.

“We have to be open-minded in how we approach kidney donation,” Dr. Vinson says. “We just need the right organ for the right patient—rather than the perfect organ—to create excellent outcomes for our patients.”
Fabry Disease

Gene therapy offers new hope for Fabry disease

After a lifetime of living with the effects of Fabry disease, Ryan Deveau is looking forward to the possibility of permanent relief. He is the fourth person in the world to take part in a Canadian phase-one clinical trial of gene therapy for Fabry disease.

“It’s like a miracle,” says Deveau, several months out from treatment. “I’m producing my own enzymes and may be able to stop the intravenous enzyme therapy I’ve been on since 2007.”

Fabry disease is a genetic disease that prevents the breakdown of certain fatty materials, due to the absence of a cellular enzyme called alpha-galactosidase.

“This fatty material accumulates in the brain, kidney, heart and other tissues, causing pain, nerve damage, heart and kidney disease, strokes and other problems,” notes Dr. Michael West, the nephrologist who approached Deveau to enroll in the CIHR-funded gene therapy trial.

Deveau was already experienced in clinical trials. He started enzyme-replacement therapy through a clinical trial more than ten years ago. His younger brother, mother and grandmother also have the disease; they, too, enrolled in that clinical trial and continue to do well on enzyme-replacement therapy.

“Everything changed for me once I started the enzyme-replacement therapy,” recalls Deveau. “Before that, even normal physical activity caused a lot of nerve pain, it wasn’t possible to manage the upkeep to own a home. Now I own a home and am married with two kids.”

The gene therapy process is complex. First, Deveau took medications to move his stem cells into his blood, so the cells could be harvested for the procedure. The stem cells were flown to Ontario, where a virus was used to put a working copy of the gene that codes for the missing enzyme into the cells. The modified cells were frozen and shipped back to Halifax to be transplanted into Deveau, who by then had received chemotherapy to knock down his own blood cell production to make room for the transplanted stem cells to graft into his bone marrow. So far, the procedure has restored enzyme production in Deveau and the other participants.

If larger-scale trials bear out the preliminary success, gene therapy could become the new gold standard for treating Fabry disease.

Ryan is the fourth person in the world to take part in gene therapy for Fabry disease which could become the new gold standard for treatment.
Researchers at NSHA who played a key role in getting a new drug approved in Canada for polycystic kidney disease are taking part in a national follow-up study of the drug’s long-term effects.

“We were one of three centres in Canada who took part in the clinical trials that led to Tolvaptan being approved in Canada in 2015,” says Dr. Steven Soroka, NSHA staff nephrologist. “The drug delays the progression of the disease, which keeps patients healthier and off dialysis longer. There’s a chance it could raise liver enzymes, though, so Health Canada granted approval on the condition that we continue to monitor patients very closely for changes in liver enzymes… they also recommended that we follow the patients as a group through a national cohort study.”

Polycystic kidney disease is a genetic disease involving 200 to 300 mutations in several genes. It is most often inherited, but as many as 10 per cent of all cases arise spontaneously in a person who has no relatives with the disease. Nova Scotia has a relatively high number of people with the disease per capita—about one in 5,000.

“The genetic mutations involved in polycystic kidney disease cause the formation of fluid-filled cysts in the kidney,” explains Dr. Soroka. “Over time, the kidneys become enlarged and their function declines… people develop high blood pressure, kidney stones and other issues, and eventually their kidneys fail and they require dialysis and/or transplant.”

Polycystic kidney disease is sometimes diagnosed in childhood, usually when a child has been screened for the disease because they have a relative who is known to be affected. More often, it is picked up in a person’s 20s or 30s, when they develop such symptoms as blood in the urine, urinary tract infection, pain in the sides or back, or an enlarged abdomen.

In addition to monitoring patients’ liver function, the national cohort study will assess their long-term health and quality of life on Tolvaptan. “We want to know how the drug affects people over time, in terms of both benefits and side effects,” says Dr. Soroka. “This is the first drug that has been shown to delay the progression of polycystic kidney disease.”
Role of Learners in Research

Learners answer key questions about activity and trauma in kidney disease

From understanding how renal disease affects a person’s response to vaccines, to its impact on use of emergency medical services and the outcomes of trauma, residents, medical students and other trainees are making significant contributions to research.

**Sedentary lifestyles compromise health**—Two trainees played pivotal roles in an NSHA Research Fund-supported project led by Dr. Tennankore that provided hemodialysis patients with accelerometers and GPS units to track the intensity and location of their physical activity. Alec Cranston, a dialysis aide now pursuing his master’s degree, worked directly with the patients, while senior resident Dr. Keigan More shaped the data into a manuscript and award-winning poster.

“This was the first project to link objectively measured physical activity to real-world locations in a cohort of dialysis patients,” notes Dr. More, who presented the work at the American Society of Nephrology in San Diego in 2018. “We learned that many patients on hemodialysis have limited physical activity. Their reduced activity likely contributes to worse outcomes and warrants a focused intervention to teach patients the benefits of even a little activity—standing sometimes rather than sitting and occasionally walking around the house, for example.”

**Impact of renal failure on outcomes in trauma**—Very little research has been done to understand how a person’s degree of renal failure impacts their risk of complications following emergency treatment for trauma. That’s why nephrology resident Dr. Ryan Pratt is working with Dr. Tennankore to link the Nova Scotia Trauma Registry and the nephrology database.

“We want to see if patients on dialysis, patients with chronic kidney disease who are not on dialysis, and patients with normal kidney function have different risk factors and outcomes of major trauma,” says Dr. Pratt. “This will help us predict which patients are most at risk for trauma and the complications that may follow.”

At the same time, the researchers are looking for any patterns of medical practice that influence the risk of complications. “It could be that the way we use certain blood products, electrolytes or fluids has an impact,” Dr. Pratt explains. “If there is anything we can change to reduce the risk of complications, we need to know.”

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Student Alec Cranston worked with dialysis patients to help gather data for the sedentary lifestyles project.
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