ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

KidneyNews

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With More High-Risk Cases, Costs of Kidney Transplantation Are Increasing

Changes in the patient population are having a major impact on the financial landscape of kidney transplantation in the United States—with higher costs but little or no change in reimbursement, according to an analysis in the *American Journal of Transplantation*.

The national retrospective cohort study examined how donor and recipient characteristics have affected the costs to transplant centers and Medicare reimbursement for kidney transplantation. The analysis included linked cost, transplant registry, and third-party payer data on nearly 54,000 deceased-donor and 37,000 living-donor kidney transplants between 2002 and 2013. The study was conducted by a team led by David A. Axelrod, MD, of the East Carolina University Brody School of Medicine Department of Surgery.

The risk profile of deceased-donor kidney transplant recipients changed dramatically during the study time period. More patients were older or had diabetes, and more transplants were performed after patients had been on dialysis for more than 5 years. Expected posttransplant survival (EPTS) score decreased, while the number of patients with high levels of allosensitization increased. A similar pattern of changes was noted for the living-donor transplant recipients. The donor population changed as well, including increased numbers of organs from older donors and other high-risk characteristics.

The cost per deceased-donor transplant (independent of acquisition costs) increased from about $98,000 in 2002–03 to $107,000 in 2012–13 (in 2013 dollars). The investigators found that the costs were significantly correlated with a wide range of recipient characteristics, including EPTS score, allosensitization, obesity, and cause of renal failure; as well as by donor characteristics, including

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Intensive Blood Pressure Control in Elderly Has Benefits—but also Possible Risks

In elderly patients with hypertension, a systolic blood pressure (BP) target of less than 140 mm Hg can improve cardiovascular outcomes. However, this intensive BP-lowering approach also carries potential risks including an increase in renal failure, according to a review and meta-analysis by Chirag Bavishi, MD, MPH, in the *Journal of the American College of Cardiology*.

Bavishi is affiliated with the Department of Cardiovascular Diseases, Mount Sinai St. Luke's & Mount Sinai West Hospitals, New York, New York.

The researchers performed a comprehensive literature review to identify randomized controlled trials evaluating the safety and efficacy of intensive versus standard or less intensive BP control for patients aged 65 years or older. Meta-analysis included data on 10,587 patients from four high-quality trials, with a mean follow-up of 3.1 years.

Efficacy outcomes included major adverse cardiovascular events, cardiovascular mortality, stroke, myocardial infarction, and heart failure. Safety evaluation included severe adverse events and the occurrence of renal failure.

In all 4 trials, the intensive therapy group achieved systolic BP of less than 140 mm Hg. Intensive BP control was associated with a 29% reduction in major adverse cardiac events (MACE), a 33% reduction in cardiovascular mortality, and a 37% reduction in heart failure.

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Inside

When stability is critical, every piece counts.

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Costs of Kidney Transplantation Are Increasing

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age, cause of death, donation after cardiac death, and terminal creatinine level; and by histocompatibility matching.

For living-donor transplants, costs increased from about $87,000 to $95,000 during the timeframe studied. Transplants with greater allosensitization were associated with higher costs for these patients. Other contributors to higher cost included obesity, cause of renal failure, the recipient's work status, and 0-ABDR mismatching.

On analysis of a subsample of about 25,000 deceased-donor transplants, adjusted Medicare payments decreased from approximately $40,000 to $34,000. Payments were minimally correlated with patient and donor characteristics. For both living- and deceased-donor transplants, payments varied significantly between regions.

"The study by Axelrod et al. addresses a very important issue of the increasing costs of kidney transplantation," said Uday Nori, MD, of the Ohio State University Wexner Medical Center. "Ever since the new UNOS conditions-of-participation for transplant centers were enforced in 2007, transplant professionals faced a great dilemma: Do we continue to provide high-risk patients access to transplantation or become risk-averse by transplanting only low-risk individuals? Ten years later the answer is still not clear."

Indeed, kidney transplantation has become increasingly complex—the result of changing demographic patterns, a shortage of high-quality organs, and increased use of treatments to address allosensitization. Transplantation improves outcomes and reduces costs, even for high-risk patients. However, these savings are only realized over time, whereas the initial costs are borne by the transplant center.

The increased cost analysis did not take into account two areas that are difficult to study, Nori said.

"In order to be compliant with the new conditions-of-participation that were enforced by CMS in 2007, most transplant centers increased their staffing in the areas of data collection, quality improvement, patient care, and administration. Professionals such as pharmacists, dieticians, social workers, and psychologists are now an integral part of the multi-disciplinary teams, which is a new paradigm in the care of transplant recipients. Among physicians, transplant trained subspecialists from nephrology, infectious diseases, endocrinology, etc., routinely provide care to these patients," Nori said. "The costs of hiring and maintaining such large highly specialized care teams is very high and adds to the bottom line for expenses for each transplant center. Although widely acknowledged, this data is not rigorously analyzed or published.

Transplantation improves outcomes and reduces costs, even for high-risk patients. However, these savings are only realized over time, whereas the initial costs are borne by the transplant center.

"The second area is the increasingly popular 'paired donor exchange' programs. With declining living donor transplants across the country, this method has gained widespread notice since 2009 or so," Nori continued. "The logistics and staffing to maintain such programs require substantial costs to the transplant centers and most likely result in net loss over time. The only major incentive for programs to do these transplants is to provide a life-saving service to an otherwise disadvantaged population and to avoid having to utilize deceased donor kidneys for these patients."

Even given these limitations, the study provides nationwide, risk-adjusted data on the association between transplant center costs and donor and recipient characteristics. The results show that costs have risen substantially along with increased numbers of nonstandard donor organs and high-risk recipients.

These changes in clinical characteristics have "eroded profitability" of kidney transplantation in the United States, the researchers said. "Policy makers should consider the creation of risk-adjusted payment for renal transplant, similar to that of liver and heart transplant, to ensure that access is reserved for expensive but deserving candidates," they wrote.

"Increasingly popular 'paired donor exchange' programs are a great example for the risk-adjusted payment model that the authors propose," Nori said.

Axelrod DA, et al. The changing financial landscape of renal transplant practice: a national cohort analysis. *Am J Transp* 2017; 17:377–389.

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Policy Update

Repeal and Replace? An Affordable Care Act Update

In January 2017, Congress decided to use the lesser known legislative vehicle called budget reconciliation for repealing the ACA. Created by the Congressional Budget Act of 1974, budget reconciliation allows for expedited consideration of certain tax, spending, and debt limit legislation. In the Senate, reconciliation bills are not subject to filibuster and the scope of amendments is limited, giving this process real advantages for enacting controversial budget and tax measures such as ACA repeal.

Congress has enacted 20 budget reconciliation bills since 1980, the first year they employed the process. Use of this less-than-common approach led some in Washington to proclaim it "flawless."

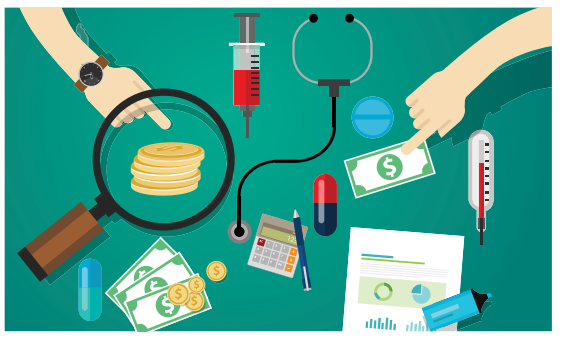
Or so they thought. The plan may still work somewhat by repealing the main provisions of the ACA, although there may be no replacement ready to take its place, leading many observers to point out that the road map to repeal is far from complete.

Expect delays ahead

After the election dust settled and the levers of power were all pointed in the direction of ACA repeal, there were some difficult realities to face. One was that some of the ACA provisions are quite popular, for example, coverage of individuals with pre-existing conditions, allowing children to remain on their parents' policy until age 26, and, in some circles, the expansion of Medicaid that now covers 70 million low-income children, pregnant women, adults, seniors, and people with disabilities.

Also, simply passing reconciliation instructions did not solve all the challenges to repealing the ACA. The very first deadline imposed by the reconciliation instructions—that the committees of jurisdiction in both chambers of Congress would report back to the Budget Committees by January 27, 2017, with their plans for ACA repeal and replace—passed quietly without comment or plans.

A couple of developments in February indicate how patchwork the repeal effort can become. On one hand, the IRS announced that it will no longer require tax filers to indicate whether they had health coverage or paid a penalty set under the ACA on their tax returns. This move effectively cuts the ACA enforcement mechanism for individual taxpayers.



On the other hand, the Trump administration offered a new Centers for Medicare & Medicaid Services (CMS) proposed rule designed to stabilize health insurance markets, which insurers claimed had been shaken by efforts to repeal the ACA, by big increases in premiums, and by the exodus of major insurers like Humana leaving some markets with only one insurer to choose from. The proposed rule would tighten certain enrollment procedures, cut the health law's open enrollment period nearly in half, and give insurers more than a month's extension on filing rates for 2018.

A very big bump in the road

If the road map to repeal is incomplete, then how Congress deals with Medicaid expansion is by far the biggest obstacle ahead.

The ACA gave states the option of expanding Medicaid, the major healthcare program for the poor and disabled, by accepting federal funds. Millions of people have gained insurance coverage after 31 states, including many with Republican governors, decided to accept the ACA terms and expand Medicaid.

This situation will pit state against state as Congress moves forward with repeal—nowhere will that dynamic be more critical than in the Senate. With Republicans in control of Congress and the White House, there is no action on ACA without Republican agreement. However, in the Senate, 20 Republican Senators represent states that expanded Medicaid that was totally subsidized by the federal government in the first 3 years of expansion. Many want to keep federal subsidies.

Conversely, 32 Senate Republicans represent states that opted out of the Medicaid expansion. Sen. John Thune (R–SD) calls it the thorniest issue of the entire debate.

"You don't want to punish or penalize states that didn't expand, but the states that did expand are going to say, 'We don't want to get punished for expanding either,'" said Sen. Thune, chair of the Senate Republican Conference.

Some in Congress want to decouple the states from the Medicaid expansion. However, rather than take the Medicare route and fully federalize Medicaid, Republicans want to transform Medicaid into block grants. This could lead to capped payments to the states or payments capped on a per beneficiary basis. Critics ask questions like: 1) What happens if there's a recession? or 2) Would the cash grant automatically increase? Other critics maintain that when Congress tried this approach with welfare reform in the 1990s, conservative states took the money and funneled it off to other projects rather than spend it on welfare enrollees.

Not even the best satellite-guided navigation system can make these detours and obstacles go away. The fate of Medicaid in the Senate may well determine the fate of coverage for millions of people—and the fate of the ACA as well.

Intensive Blood Pressure Control

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There was no significant difference in the outcomes of myocardial infarction or stroke.

A random-effects model found no difference in serious adverse events or renal failure between treatments, the researchers said. However, in a fixed-effects model, intensive BP lowering was associated with a significant, twofold increase in the risk of renal failure.

On meta-regression analysis, MACE risk decreased by 3 percentage points for each 1 mm Hg difference in mean achieved systolic BP. The reserachers noticed a similar association for cardiovascular mortality, but not for serious adverse events or renal failure.

The optimal target BP for patients with hypertension is a topic of ongoing controversy. In 2014, the Eighth Joint National Committee recommended a systolic BP target of less than 150 mm Hg in patients aged 60 years or older, compared to the previous target of 140 mm Hg.

The new analysis of high-quality randomized trial data shows that intensive BP reduction in patients aged 65 or older is associated with reductions in MACE, heart failure, and cardiovascular mortality. Although data on adverse events remain limited, Bavishi and his colleagues said, these data suggest a possible increased risk of renal failure at the lower BP target.

Other concerns regarding intensive therapy in this age group include an increased number of antihypertensive drugs and possible increases in other adverse events, including hypotension and syncope. The investigators conclude, "When considering intensive BP control, clinicians should carefully weigh benefits against potential risks"

Bavishi C, et al. Outcomes of intensive blood pressure lowering in older hypertensive patients. *J Am Coll Cardiol* 2017; 69:486–493.

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

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

ASN President's Column

Eleanor Lederer, MD, FASN

ASN President Eleanor Lederer, MD, FASN, spoke with ASN Executive Vice President Tod Ibrahim for the first of a series of podcasts to be available through Kidney News Online throughout 2017. Here Kidney News *presents excerpts from the podcast, including why Dr. Lederer chose nephrology and her thoughts on some of the most exciting areas of research into kidney diseases.*

Dr. Lederer is Professor of Medicine at the University of Louisville School of Medicine, Chief of the Division of Nephrology, Associate Director of the Nephrology Fellowship Training Program, Associate Chief of Staff for Research and Development at the Robley Rex VA Medical Center, Director of the Metabolic Stone Clinic, and Associate Ombudsman for the medical school. Her research centers on regulation of the sodium phosphate transporter in proximal renal tubules. Dr. Lederer is board certified in internal medicine and nephrology, and is a UNOS-certified transplant physician. In addition to participating in many ASN committees, Dr. Lederer has served on the ASN Council since 2011. She became ASN President January 1, 2017.

TOD IBRAHIM

I'm curious, when did you decide to become a nephrologist?

ELEANOR LEDERER

It wasn't until my third year of residency. Actually, I was interviewing for positions in internal medicine private practice in Houston, which is where I trained, at Baylor College of Medicine. I had one month during which I was rounding on the general medicine service at our county hospital. My attending was the chief of the renal division, Wadi Suki. It was one of those months that it seemed every other patient was a kidney patient. We had cases of malignant hypertension, flagrant lupus nephritis, a patient with membranous glomerulopathy who ended up with a renal vein thrombosis—some very unusual types of cases. At the end of the rotation, Dr. Suki turned to me and said, "You seem to like nephrology. Do you want to be a renal fellow?"

I thought about it for maybe five minutes, and then said, "Sure." I really had never considered it before, but I haven't regretted it for a moment since. For the record, that was 1981, clearly another downtime, I guess you would call it, for interest in nephrology, because if I had not agreed to become a renal fellow that year, they would have had only one first-year renal fellow for a huge program that covered three giant hospitals. So that was a time when nephrology was not that attractive to residents. I believe it's cyclical.

TOD IBRAHIM

Mentorship and role modeling are really important. What did you learn from Dr. Suki?

ELEANOR LEDERER

First of all, he was known as a researcher in divalent ion metabolism. But his approach to patients was what really grabbed me. He could take basic renal physiology and apply it to the patient in front of him. He also had a way of being able to look at the whole patient, but then to dissect out the problems on a one-by-one basis and tackle each of them. He was not the only one who did this—several other members of the renal division could do the same thing, and I found that amazing. I really liked the fact that the approach to the patient was thoughtful and logical, that you looked at the whole patient and not just a single organ. But then you were also able to understand, at a basic physiological level, what was going on for a particular nephrology issue. And I told myself, that's the way I wanted to be. I wanted to be able to do the same thing.

TOD IBRAHIM

And you have done that. I know you have a big clinical load, so you see a lot of patients, but you also run a basic science lab. What is similar and what has changed between, say, where Dr. Suki was in the early '80s and where you are now near the end of the 2010s.

ELEANOR LEDERER

Grant funding is a lot harder to get now, and actually, there is quite a bit that has changed. Interestingly, the academic setup at Baylor was quite similar to what it is at the University of Louisville: a medical school that is affiliated with a number of different hospitals, both public and private, with the same sorts of tensions that exist when you have an administration of a private hospital, perhaps having a different agenda or different priorities than a medical school.

But yes, research funding was a lot easier to come by during the '80s. I won't say that everybody always had a grant, but Dr. Suki had research grants for a considerable amount of the time I was there. I'm not sure exactly what the funding level was, but I've heard quotes that it was in the 30th percentile, and that, of course, is considerably different from what it is now.

The types of patients we were seeing were actually extraordinarily similar to those we see now, so I don't think that has changed very much. What has changed is where these patients are taken care of. When I was in training, you could admit someone with practically anything to the hospital. If a person had a bad headache, you could get them admitted. When we saw somebody who had proteinuria as an outpatient, we could admit them for their entire proteinuria workup, including the biopsy, wait until the results of the biopsy came back, and start them on therapy. That doesn't happen now.

One of the advantages for a trainee in having that opportunity was that you were able to see very easily, unfolding right in front of you, how you do a workup on a certain clinical problem all the way to the very end to treatment. I think this is more challenging now, because you don't want to admit a patient for an entire workup. Most of the workup is done in the outpatient setting. The patient may or may not even be admitted for the biopsy. Then they come back to clinic where the decision on treatment is being made. So it may be a little harder now for trainees to get the total evolution of an evaluation of a patient.

TOD IBRAHIM

From your perspective, what are some of the most exciting areas of research into kidney diseases?

ELEANOR LEDERER

There are a lot of exciting areas of research. I guess the first one that pops into my mind is the discovery of the variations in the *APOL1* gene and the propensity for the development of kidney disease in African Americans. To me, this discovery started to provide an answer to a question that so many of us had asked for many years: Why was it, when you looked at the dialysis population, that African Americans were disproportionately represented? Some very nice studies done early on suggested that even when you held many other factors constant, such as blood pressure control, diet, where they lived, profession, and socioeconomic status, that still, African Americans progressed to end stage kidney disease more often than Caucasians did. The discovery that the variations in this gene can confer some propensity toward the development of kidney failure, I think, from a public health standpoint, is just phenomenal.

The next step is to figure out what exactly happens. What is the mechanism by which changes in this one protein can have such a profound effect on kidney health, and what can we do about it? Is this a gene therapy thing or would this be amenable to more conventional pharmacologic therapies? The *APOL1* finding, to me, stands out as number one.

Another exciting shift in the way that we think about kidney diseases is exemplified by the discovery that the antigen that produces, or antibodies against the antigen that produces, membranous glomerulonephritis is PLAR2. This finding got everyone to start thinking more about the glomerular diseases apart from their simple pathology. The pathology has done well for the years that we've used it. You look at the pathology and see a pattern (the name of the disease is actually based on the pattern seen on pathology), but all of us knew that's what we were doing. We were looking at the picture, describing the picture, and calling it the disease.

Discovering what appears to be a causative protein has allowed us to start thinking in terms of pathophysiology, not simple pathology. We see this extending from the discovery in membranous glomerulopathy to the complement-associated kidney diseases, and, now, to what is in essence, an entire reorganization and reclassification of what we used to call membrano-proliferative glomerulonephritis, which is now being subclassified into a more mechanistic type of organization as opposed to a simple picture. This is the same thing we see with IgA nephropathy, and the next big one that's going to fall is focal segmental glomerulosclerosis. We already know from studies, some of them from the University of Louisville and other places, that there are differences in the composition of the matrix tissue deposited in focal segmental glomerulosclerosis in the different types, and this again, points toward the fact that we have lumped a bunch of things together based on what the pathology picture looked like. Now we are going to be able to completely reclassify these illnesses, which then points toward much more individualized therapies for them. This is another big shift in the way nephrology is happening.

I think there are two other areas. First, "How does acute kidney injury (AKI) result in chronic kidney disease?" This is something new and exciting. I can tell you that when I was in training, the teaching was that you get AKI and you're going to get better from it. We now know that, sure, you'll be able to come off dialysis if you required it for the AKI, but there are some subtle changes that occur, and these subtle changes, over time, can lead to the development of chronic kidney disease.

As a sequel to that question, another exciting area of research is understanding the mechanisms by which chronic kidney disease leads to myriad systemic effects. Over the past 10 years, we had the discovery of FGF-23 and what it does to produce left ventricular hypertrophy. We had the discovery of the inhibitors of WNT signaling that contribute to bone disease and the loss of Klotho . . . who knew in a million years that there was a protein produced and expressed in the kidney that would have such myriad systemic effects? And yet it's interesting that even when I was in fellowship training from 1981 to 1984, my mentors and others were describing chronic kidney disease as accelerated aging. And we now know from the discovery of Klotho, that in fact in many ways, they were absolutely correct because chronic kidney disease results in the loss of Klotho, and the loss of Klotho is one of the major contributors toward aging. This, to me, is very exciting.

The last piece of exciting research I would like to touch on is that, in 1984, if someone had told me dietary potassium regulates the expression of the sodium chloride co-transporter, I would have told them they were crazy. And yet we now see discoveries of entirely new signaling systems that have allowed us to understand sodium and potassium handling in the kidney so much better—just when many people thought, "Oh, this is done. We've done sodium–potassium, we know how this works."

I think there is a tremendous amount of new knowledge in nephrology. I think there are many exciting things right on the edge of happening, and the discoveries that I've talked about are the first steps leading to very exciting and innovative therapies for these illnesses. I think that in the next 10 years we will see a phenomenal explosion of new therapies for kidney diseases.

Findings

Self-Management Support in CKD: Patients' Viewpoints

Patients with chronic kidney disease (CKD) need a "multimodal, person-centered framework" to support disease self-management, with a special focus on everyday strategies, according to a study in *BMC Nephrology*.

The cross-sectional survey study solicited Australian CKD patients' views on their desires for support in self-management of their disease. Thirty-six patients filled out a paper survey at a primary care clinic, and another 61 patients completed an online survey.

About 60% of respondents were women; mean age was 56 years and mean time since diagnosis 8 years. The patients expressed the wish for more support in 10 previously identified aspects of self-management, with the highest rating for "keeping a positive attitude taking care of mental and physical health." Other highly rated areas included "actively participating in healthcare," "CKD-specific knowledge," and "noticing and treating signs and symptoms." Individual patients identified other areas in which they wished for more support.

Young patients expressed a stronger desire for additional support, as did better-educated, employed, and female patients and those with a longer time since diagnosis. About 70% of patients said they would be willing to attend self-management support sessions during work hours. Patients identified a range of potentially helpful methods of information delivery, including written materials and online contact.

The study provides new insight into the self-management needs and preferences of patients living with CKD. "The findings . . . highlight the need for person-centered care and patient engagement in the renal world, as different groups of patients vary in their overall enthusiasm for learning more about effective self-management," the researchers write. Patient education should focus on everyday strategies—not just information on CKD and medications [Havas K, et al. Person-centered care in chronic kidney disease: a cross-sectional study of patients' desires for self-management support. *BMC Nephrol* 2018; 18:17].

No Benefit of Tight Glycemic Control in Critically Ill Children

Tight glycemic control—with a blood glucose target of 80 to 110 mg/dL—does not improve outcomes for critically ill children, concludes a trial in *The New England Journal of Medicine*.

The randomized, multicenter trial included 713 critically ill children with confirmed hyperglycemia, excluding cardiac surgery patients. Patients were assigned a target blood glucose range of 80 to 100 mg/dL (tight glycemic control) or 150 to 180 mg/dL. The study included continuous glucose monitoring with explicitly guided insulin adjustments. The main outcome of interest was number of ICU-free days up to day 28.

Recruitment was halted at 50% enrollment when data and safety monitoring suggested a low chance of benefit plus evidence of possible harm. On intention-to-treat analysis, median number of ICU-free days was about 19 in both groups. Secondary outcomes—including mortality, severity of organ dysfunction, and ventilator-free days—were similar as well.

Evidence of harm in the tight glycemic control group included an increased risk of healthcare-associated infections: 3.4% versus 1.1%. Patients assigned to the lower glucose target were also at higher risk of severe hypoglycemia (less than 40 mg/dL): 5.2% versus 2.0%.

Previous studies have found no clinical benefit of tight glycemic control in critically ill adults or in children after cardiac surgery. The new results find no improvement in outcomes with a blood glucose target of 80 to 110 mg/dL in critically ill children without cardiac surgery. Tight control may also increase the risk of adverse outcomes, including hypoglycemia and catheter-associated bloodstream infections [Agus MSD, et al. Tight glycemic control in critically ill children. *N Engl J Med.* January 24, 2017; DOI: 10.1056/NEJMoa1612348017].

Does HLA-Incompatible Kidney Transplant Improve Survival?

For highly sensitized patients on the UK transplant waiting list, HLA-incompatible (HLAi) kidney transplantation does not improve survival, compared to patients who remain on dialysis, reports a study in *The Lancet*.

From more than 25,500 patients on the UK transplant waiting list, the researchers identified 213 patients who underwent HLAi kidney transplantation from 2007 through 2013. Two-thirds of the recipients were female. Median age at transplantation was 44 years and median calculation reaction frequency 96%.

The HLAi transplant recipients were matched in a 1:4 ratio to patients who had a similar degree of sensitization and were listed for deceased-donor transplantation during the same period. Patient survival was compared between the HLAi and matched cohorts, with follow-up through 2014.

Of the 852 patients in the matched cohort, 41% had still not received a transplant at 58 months' follow-up. Overall survival was not significantly different for the HLAi transplant patients versus those in the matched cohort, either listed or transplanted. The HLAi transplant group consistently had the lowest death-censored graft survival: 68% at 5 years, compared to 89% for those with compatible living donors and 77% for those with compatible deceased donors.

More than 40% of patients on the UK kidney transplant waiting list are HLA-sensitized, and this group has a much longer waiting time compared to unsensitized patients. Desensitization followed by HLAi transplantation is an option, but there are limited data on patient survival.

This matched cohort study provides a "circumspect view" of the outcomes of HLAi kidney transplant in the United Kingdom. Survival is similar to that of sensitized patients who remain on dialysis while awaiting a compatible kidney, many of whom are unlikely to receive a transplant. The authors note that their findings contrast with a recent US multicenter study [Manook M, et al. Post-listing survival for highly sensitized patients on the UK kidney transplant waiting list: a matched cohort analysis. *Lancet.* 2017; doi: 10.1016/S0140-6736(16)31595-1].

High Prevalence of Diabetes among People with HIV

Diabetes is present in one-tenth of US adults being treated for HIV infection, suggests a study in *BMJ Open Diabetes Research & Care*.

The researchers compared the weighted prevalence of diabetes in two populations from nationally representative studies: 8610 HIV-infected adults from the Medical Monitoring Project and 5604 general population subjects from the National Health and Nutrition Survey (2009-10 data from both studies). Diabetes was assessed as a physician diagnosis or use of medications for diabetes.

The unadjusted prevalence of diabetes among HIV-positive adults was 10.3%, compared to 8.3% in the general population sample. On adjusted analysis, diabetes prevalence was 3.8% higher in HIV-infected adults. Subgroups of HIV-positive subjects showed even larger differences: 5.0% in women, 4.1% in those aged 20 to 44, and 3.5% in nonobese subjects. Factors independently associated with diabetes in the HIV-positive population included older age, obesity, longer time since HIV diagnosis, and geometric mean CD4 cell count.

As patients with HIV infection live longer, they are at risk of chronic metabolic and cardiovascular diseases. The new study shows that US adults with HIV infection have an increased prevalence of diabetes compared to the general population.

Adults with HIV are more likely to deveop diabetes at younger age and in the absence of obesity. The authors suggest further studies to determine whether HIV should be regarded as an additional risk factor for diabetes, and to identify optimal treatment strategies for HIV-positive diabetic patients [Hernandez-Romieu AC, et al. Is diabetes prevalence higher among HIV-infected individuals compared with the general population? Evidence from MMP and NHANES 2009–2010. *BMJ Open Diabetes Research and Care*. 2017; 5:e000304. doi: 10.1136/bmjdrc-2016-000304].

No Reduction in Cardiac Surgery–Related AKI with Spironolactone

The mineralocorticoid receptor blocker spironolactone does not reduce the risk of acute kidney injury (AKI) in patients undergoing cardiac surgery, concludes a trial in *American Journal of Kidney Diseases*.

The randomized, double-blind trial included 233 adults (mean age 53) undergoing cardiac surgery with cardiopulmonary bypass. Starting the day before surgery, one group received spironolactone—100 mg, with three further 25 mg doses given on postoperative days 0, 1, and 2—while the other group received placebo. Patient characteristics were similar between groups: mean serum creatinine level was 0.9 mg/d, while the median Thakar score (used to estimate AKI risk) was 2. Patients were followed up for 7 days, or until ICU discharge.

Acute kidney injury occurred in 43% of patients assigned to spironolactone versus 29% in the placebo group. The difference was not significant on adjusted analysis, although "the odds ratio showed a propensity toward risk."

The spironolactone and placebo groups had a similar incidence of stage 2 and 3 AKI. Secondary outcomes were also similar, including renal replacement therapy, length of ICU stay, and mortality.

Aldosterone could play a role in kidney injury during renal ischemia. In rat models, the authors have found that spironolactone can prevent renal injury induced by ischemia-reperfusion.

However, this randomized trial finds no renoprotective effect of spironolactone in reducing the risk of AKI after cardiac surgery. However, it suggests a possible trend toward increased risk. The authors discuss possible reasons for the discordant results from their preclinical studies [Barba-Navarro R, et al. The effect of spironolactone on acute kidney injury after cardiac surgery: a randomized, placebo-controlled trial. *Am J Kidney Dis* 2017; 69:192–199].

High Distress among Undocumented Immigrants with ESRD

Undocumented immigrants with end-stage renal disease (ESRD) suffer from serious physical symptoms and psychosocial distress—particularly related to receiving hemodialysis on an "emergent-only" basis, reports a qualitative study in *JAMA Internal Medicine*.

The investigators performed semi-structured interviews with 20 undocumented Latino patients with ESRD seen at a safety-net hospital in Colorado. The patients were 10 men and 10 women, mean age 51 years. All had been in the United States for at least 5 years before ESRD diagnosis.

Analysis of interviews identified themes in four major categories. Patients experienced a gradual and distressing increase in symptoms after emergency hemodialysis, identifying dyspnea as the most burdensome symptom. Because of high patient volume and inconsistent admission criteria, they had uncertain access even to emergent hemodialysis. To avoid being turned away at the hospital, some patients reported waiting until symptoms were severe enough to put them at risk of death.

The patients experienced high anxiety about their risk of death as symptoms accumulated. They described comforting relationships with other patients and suffered distress when those people died. They discussed the impact of emergent-only hemodialysis on their families, and the importance of family caregivers.

Patients understood that they were receiving suboptimal care owing to their undocumented immigration status, the investigators said. Many had a willing donor, but lacked access to transplantation. Participants said they appreciated the kindness and empathy of providers at the safety-net hospital.

The findings highlight the high symptom burden experienced by undocumented immigrants with ESRD who lack access to scheduled hemodialysis.

"This distress, coupled with higher costs for emergent dialysis, indicate that we should reconsider our professional and societal approach to ESRD care for undocumented patients," the researchers said [Cervantes L, et al. The illness experience of undocumented immigrants with end-stage renal disease. *JAMA Intern Med.* Published online February 6, 2017. doi:10.1001/jamainternmed.2016.8865].

Renal Biopsy Detects Nondiabetic Kidney Disease in Diabetic Patients

Renal biopsy can be useful in establishing the correct diagnosis and treatment in patients with diabetes—a population with a high prevalence of nondiabetic renal disease (NDRD), according to a meta-analysis in *Nephrology Dialysis Transplantation*.

The researchers identified and analyzed data on the frequency of diabetic nephropathy, NDRD, and "mixed" forms of kidney disease among patients with diabetes. The analysis included data on 4876 patients undergoing renal biopsy, reported in 48 studies.

For all three diagnostic categories, prevalence varied widely: from 6.5% to 94% for diabetic nephropathy, 3.0% to 82.9% for NDRD, and 4.0% to 45.5% for mixed kidney disease. IgA nephropathy was the most common NDRD diagnosis in 16 studies, membranous nephropathy in 9, focal segmental glomerulosclerosis in 6, and acute interstitial nephritis in 4.

The positive predictive value of renal biopsy was 50.1% for diabetic nephropathy, 36.9% for NDRD, 19.7% for mixed diagnoses, and 49.2% for the combination of nondiabetic and mixed kidney disease. On metaregression, factors explaining heterogeneity for NDRD were systolic blood pressure, HbA1c, duration of diabetes, and diabetic retinopathy. In contrast, for diabetic nephropathy, serum creatinine was the only explanatory factor. Crude odds ratio for detecting diabetic nephropathy at renal biopsy was 69% higher than that for NDRD, and more than four times higher than that for mixed kidney disease.

There is ongoing controversy over the value of renal biopsy in patients with diabetes; its performance is commonly based on opinion or institutional policy. Rapidly declining kidney function or unusual clinical features in diabetic patients may lead to a "clinical diagnosis" of diabetic nephropathy. However, many such patients may have NDRD or a mixed diagnosis requiring different management.

This review and meta-analysis suggests a "seriously high" prevalence of NDRD on renal biopsy in patients with suspected diabetic nephropathy.

"Clinical judgment alone can lead to wrong diagnoses and delay the establishment of adequate therapies," the researchers write. They highlight the need for further studies to better identify patients who can benefit from renal biopsy [Fiorentino M, et al. Renal biopsy in patients with diabetes: a pooled meta-analysis of 48 studies. *Nephrol Dial Transplant* 2017; 32:97–110].

In-Center Self-Care Hemodialysis: **An Idea Whose Time Has Come?**

Leslie Trigg

In this issue, Kidney News *interviewed Leslie Trigg, President and CEO, Outset Medical, about the company's focus on in-center, self-care hemodialysis.*

What spurred your interest in Outset Medical?

Most of my medical device career has been in spent in areas of healthcare that have experienced rapid, technology-driven change. In cardiology, for example, it's not unusual to see several groundbreaking new devices enter the market in the same year. What hit me right away about dialysis was the inverse. The paucity of new technologies was striking. Being new to it, I thought, "Well, is new technology needed? Maybe there are no unmet needs that can be solved by technology." Those questions were quickly answered by learning more about the clear need for cost reduction and improvement of the patient experience.

We see an exciting opportunity for technology to help solve important problems within dialysis care provided in clinics, in hospitals, in homes, and in extended care facilities.

I understand the Tablo hemodialysis system was first designed solely for the home dialysis market. Why the shift to in-center self-care hemodialysis?

There are many home hemodialysis benefits to patients. For example, increased flexibility, increased independence, and increased control all lead to significant improvements in well-being. The problem is that so few patients are able to enjoy these benefits because today they are only available if the patient chooses to go home. And there are very real barriers to home hemodialysis that prevent many patients from being able to choose it: living alone, not wanting to dialyze more frequently, not having space, and fear of needles, to name a few.

This conundrum got us thinking about a broader question, "How can we increase patient access to increase control, independence, and flexibility?" And it led us to an idea … creating a new modality of care in the clinic that would offer many of the benefits of home, but without any of the barriers *to* home.

There are many advantages to the clinic model for patients—the social networking with other patients, and clinical support and oversight by nurses and technicians, to name a few. What can be added to these benefits through self-care is greater ownership and empowerment for patients.

What are the benefits of in-center self-care to patients?

Patients who have experienced in-center self-care using Tablo have talked about feeling more in control and having a greater sense of confidence and self-worth. One patient noted, "It makes me feel proud to walk in the dialysis clinic and set up Tablo all on my own, with other patients watching."

In terms of control, the ability of a patient to understand and resolve alarms without waiting for a technician to help is a big deal to people. A patient once told me: "Nobody cares more about me, than me." Having the ability to respond immediately to physical symptoms you might be feeling (such as cramping or headaches) and having the knowledge of how to do that, aided by automating technology, is empowering.

Not waiting for technician help during treatments is a part of a larger benefit—reducing wait time in the clinic overall. Based on analysis of treatments completed on Tablo, we found that for the vast majority of individuals, it takes 10 to 15 minutes. Because patients are in control of how quickly they get set up and are ready to begin treatment, there's obviously an opportunity to minimize wait times both getting on and getting off dialysis. Each patient is only responsible for herself, compared with a patient care technician who is responsible for getting four patients on and four patients off dialysis.

In the future, we intend to study whether in-center self-care results in fewer hospitalization days for patients. A number of studies performed outside of dialysis in asthma, diabetes, and hypertension demonstrate that higher patient engagement, also known as patient activation, results in fewer hospitalization and ER visits, and lower costs (1).

In a recent interview, you mentioned that shifting from full in-center dialysis to in-center self-care can be compared somewhat to the shift from full-service to self-service gas stations. What corollaries can be drawn?

Another analogy drawn from consumer life is the self-checkout lines in retail stores. When first introduced, consumer resistance in early adopter stores like Home Depot was high. And initially, it was less efficient for retailers because the workflow was different and behavior change was needed, not only among consumers, but among the retailer's own staff too. Over time, as learning occurred and the workflow was optimized, self-checkout became normative to the point that retailers like Amazon Go have introduced stores that only offer self-checkout, and everyone is comfortable with it.

We expect a similar experience for clinics implementing in-center self-care. At first, it's new and it feels uncomfortable, particularly within a service model that hasn't changed much over the past 30 years. Patients, clinic staff, and physicians all need to think a little differently about their respective roles. Efficiency gains aren't obvious because the operational workflow is different and isn't fully optimized. Yet for clinics with an innovative mindset, they see the opportunity to push through frustrations and unexpected challenges in order to get to the upside—a new model of care that both reduces costs and dramatically improves the patient's experience.

What other areas of medicine might be examples of in-center self-care?

Providing patients with independent care ownership is occurring throughout healthcare at an increasing pace. Diabetes care stands out as one obvious example. New technologies that combine glucose monitoring with automated insulin delivery and mobile data allow diabetic patients real-time access to information and the ability to act on it independently, resulting in empowerment and control. In Europe, self-serve diabetic management kiosks allow diabetic or pre-diabetic patients to come in on their own schedule and independently perform a foot scan to screen for diabetic foot problems, HbA1c, a retinal scan, creatinine level check, and other monitoring tests.

What is the evidence for in-center hemodialysis self-care?

An article by Dr. Edward Jones and colleagues in *Nephrology News & Issues* described his clinic's long-term experience with in-center self-care. Clinical outcomes for in-center self-care patients were compared to conventional hemodialysis patients treated within the same provider network within the same geographic area, using a propensity-score methodology. The data showed that in-center self-care patients had fewer hospitalization events (0.82 vs. 1.7 per patient year; $p=0.008$) as well as fewer missed treatments (1.1% vs. 3.8% of all treatments; $p<0.05$), and a lower mortality rate (0.02 vs. 0.07 per patient year; $p=0.005$).

With tangible clinical benefits of in-center self-care emerging in the literature, the question then becomes what changes are needed to expand access to a greater number of patients. This is where we believe Tablo can help.

By designing a friendly "consumer version" of a dialysis machine, we had several goals in mind: 1) remove the intimidation factor; 2) simplify and expedite setup; and 3) reduce nuisance alarms such that patients could remain independent throughout the treatment. These design goals are

embedded in Tablo. Easier, automated technology means a large percentage of the dialysis population is now capable of setting up and managing the treatment on their own.

What is a key challenge to in-center self-care, and how is Outset aiming to shift the curve and address it?

One of the understandable question marks about in-center self-care in concept is training. Home hemodialysis training consumes several weeks and dozens of hours to educate just one patient. So naturally, when you are now talking about training dozens of patients for self-care inside a given clinic, concerns emerge about how much staff time it will consume to educate them all.

Most of what patients have to learn about Tablo revolves around getting comfortable with a tablet since Tablo's setup is guided by illustrations and videos displayed on a large touchscreen. Teaching people how to interact with a tablet using a paper training binder didn't make much sense to us, especially because it would require lots of staff time. Instead, we developed a proprietary training app that patients work on independently while they are dialyzing (on any machine) and before they start self-care. The game-ified content approach keeps the experience entertaining while also measuring the patient's cognitive abilities through comprehensive quizzes along the way. With independent learning, Tablo self-care training becomes scalable without staffing becoming a bottleneck.

Tell us more about the dropout rates from home hemodialysis (HHD) and how Outset's system can help.

Before we talk about dropout, let's discuss patient adoption. The home hemodialysis needle has not moved much in years, hovering around 1.5% penetration. Why? Our attention has been on identifying the barriers to adoption and determining how Tablo can help on the front end. Some of the concerns patients wrestle with during decision-making include a daunting amount of HHD training time, fear of cannulation, and the prospect of having to dialyze more frequently than in-center. We decided to attack the training barrier by developing a self-guided patient training app that results in total training time measured in hours, not weeks and months. In terms of the treatment frequency barrier, Tablo offers flexibility. Patients can continue dialyzing five or six times a week, but they also can dialyze three times per week or every other day if desired and clinically appropriate. We see an opportunity to expand HHD penetration, particularly with a technology that helps eliminate the barriers.

In terms of retention, studies and market research on home hemodialysis consistently indicate that the high dropout rate is fueled by a number of factors such as having to do dialysis more frequently than in-center, having to spend significant time making the dialysate in advance of treatment, having to store supplies, and other frustrations that lead to patient and caregiver burnout. Tablo helps address these pain points for patients by, for example, automatically purifying water and producing dialysate on-demand while the patient is dialyzing, and by automating much of the setup, so that it is faster for the patient to get started. These features offer patients more flexibility when they dialyze. The simplicity of the steps is aimed at minimizing the hassle factor that often leads to frustration and burnout, and, it is hoped, will make home hemodialysis more manageable and sustainable for patients over time.

Do you foresee people who start with a system like yours in-center ultimately being able to move to HHD?

It's certainly possible that in-center self-care ultimately might serve as a "bridge to home" for some patients. It gives people a stepping stone to independence without immediately throwing them in the deep end of the pool. For many patients though, the ability to have more flexibility and control over their treatment, but in the clinic setting where they don't need a care partner and they don't have to self-cannulate, is going to be a desirable long-term option.

Talk about the data aspect of Tablo, both with regard to providing feedback to clinicians on clinical outcomes, and to the patient, who'd like to know how they are doing.

Tablo has the ability to wirelessly transmit data in two directions: *to* Tablo and *from* Tablo. After each treatment, the flowsheet can be sent up to the Cloud and pulled down directly into a provider's EMR. By sending treatment data automatically, and directly (vs. a tablet-based solution), patients don't have to get involved with it, thereby saving time and avoiding complexity.

Going the other way, the patient's prescription can be sent wirelessly from the provider's EMR directly to the Tablo on which the patient is dialyzing. Two-way transmission also allows us to wirelessly update content and provide software updates with new features and functions.

Providing treatment data to patients is in our future and something we believe offers tremendous value, particularly in concert with in-center self-care. Drawing again on the diabetes space, we've seen how powerful it is for patients to have immediate access to their glucose levels, for example, and the ability to use that data to make smart food and lifestyle choices in the moment. We view a similar opportunity for dialysis patients who, to date, have not had access to much data.

What is next in your rollout? How do plan to scale up?

For the foreseeable future, we're going to pursue a thoughtful, methodical pace to our expansion. We're very cognizant of the inherent challenges that come with introducing both a new device and a new modality of care all at the same time. There's a lot to learn all around in order to reach the point where there is broad muscle memory around how to effectively implement in-center self-care. The most important goals for us to reach near-term are to ensure that patients enjoy their experience on Tablo and their experience with self-care, and that physicians and clinical staff see patients feeling well and perhaps, even better, than on traditional care.

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Before becoming Outset Medical's president and CEO, Leslie Trigg served as an Executive-in-Residence at Warburg Pincus. Prior to that she was executive vice president at Lutonix, a cardiovascular medical device company acquired by CR Bard, and before joining Lutonix, Leslie served as chief business officer of AccessClosure, a vascular closure company acquired by Cardinal Health. Earlier in her career, she held senior leadership positions at FoxHollow Technologies, Cytyc Corporation and Pro-Duct Health, Inc. (acquired by Cytyc). She began her medical device career at Guidant Corporation in new product global marketing. In addition to her role at Outset she is a board member of Cardiovascular Systems, Inc.

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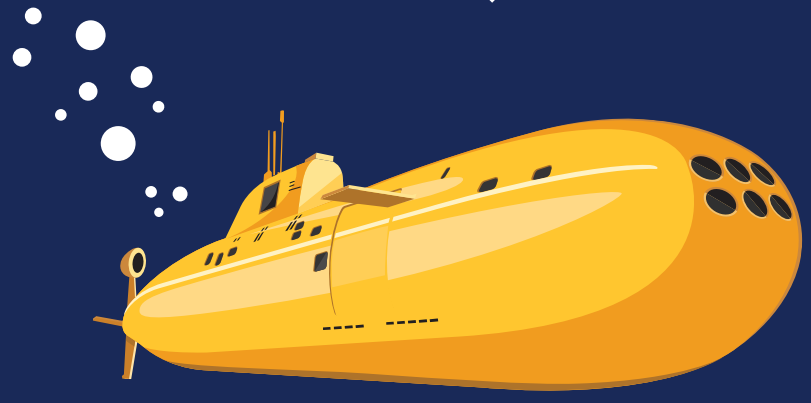

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ASN Communities Mark One Year Anniversary

By Zach Cahill

To increase inclusivity and accessibility, the American Society of Nephrology (ASN) introduced a new member benefit in March 2016: an online community.

As ASN has grown, it has become even more important to leverage the society's diverse and global membership. Filling that need requires a digital platform where all members can network, collaborate, discuss, and lead around important issues facing nephrology.

One year since implementation, ASN Communities continue to evolve to provide members opportunities to network and collaborate. Rather than being rigid, ASN Communities seek to be responsive and bottom up, providing a venue for the society's members to set their own agendas and pursue what they care about. Before Communities, the average ASN member had few opportunities to be involved with the society and even fewer avenues to connect with fellow members. Now, all members can meet outside ASN Kidney Week and lead in any area of interest.

ASN Communities are a central hub for members to tap into the diversity of expertise in the field of nephrology. By providing intuitive ways to talk with others via discussion threads, posts, and direct messages, members communicate with each other. Discovering others via profiles, sharing your work via libraries, and enjoying focused discussion in diverse communities all facilitate collaboration.

The Communities have covered significant ground over the past year. The platform has emerged as an important part of the lives of international members. In 2016, 20% of Communities contributors were international members, who accounted for 21% of total logins. A critical part of initiating the new ASN Strategic Plan was establishing inclusive communities with dedicated leaders and agendas to serve the varied interests of the society's members. To that end, ASN Communities now offer 11 communities with 34 leaders and 5853 total posts. The Open Forum hosts dozens of issues not yet represented in separate communities.

ASN Communities provide a platform to discuss many critical issues, including the American Board of Internal Medicine's Maintenance of Certification Program, interest in nephrology careers, basic science, and much more. Many members visit the site to get help on cases, providing the opportunity for educational discussions about best practices and the latest evidence.

Coinciding with the one-year anniversary, ASN is simplifying the process to open new communities and revamping the role of community leaders. Other enhancements include adding interest codes to profiles, a best answer button to posts, and a section of the homepage devoted to the most popular threads. In 2017, ASN hopes to highlight international members, offer more events, and ensure communities have a bigger presence at ASN Kidney Week 2017, which will take place October 31 to November 5, in New Orleans, LA.

Launching ASN Communities could not have happened without members willing to take a risk on a new platform and give their time to make an experiment work. Special thanks to the community leaders, most active members, and beta testers. ASN Communities are the society's members, and ASN looks forward to more growth and engagement in 2017.

Zach Cahill is Communities Associate at the American Society of Nephrology

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ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Fellows Corner

In this article, fellows Arpita Basu, MD, MPH, and Rob Rope, MD, address the advantages and disadvantages of mandating procedural competency in nephrology fellowship.

Mandating Procedural Competency in Nephrology Fellowship: Necessary or a Loss of Time?

By Arpita Basu, MD, MPH, and Rob Rope, MD

Too little time, too much to learn?

Procedures have played an integral part throughout the practice of nephrology. However, it is time to evaluate this tradition. Competency in our "core" procedures (e.g., kidney biopsies and non-tunneled hemodialysis catheter placement) is required by the Accreditation Council for Graduate Medical Education (ACGME) for graduation from nephrology fellowship, although there is no minimum requirement for the number of procedures to be performed (1). Between juggling consults, racing through clinics, performing research, or getting some reading done, is there any time left for procedures?

In the "real" world, owing to time constraints, turf battles, and proficiency concerns, only a limited number of nephrologists perform a few select procedures. These procedures are now increasingly performed by other specialties or by interventional nephrologists. This raises a nagging question: Is expertise in these procedures vital for a budding nephrologist?

If we are to maintain these competencies, it must be recognized that our national performance is suboptimal. Surveys conducted in the past decade have highlighted the limited training in procedures obtained during fellowship and the discomfort many independent nephrologists feel while performing them. In 2008, a survey by Berns and O'Neil showed that while core procedures were a part of almost all fellowship curriculums, the training obtained was not consistent across programs (2). Other studies have reported that 33% of practicing nephrologists did not feel comfortable placing temporary HD catheters, and of the graduating fellows, 25% had not placed a temporary IJ catheter, 15% had not placed a femoral catheter, and 5% had never done a renal biopsy (3,4). With ACGME proficiency requirements still in place, how is it that so many fellows graduate without performing the required procedures? If these skills are mere checks in checkboxes essential to graduation, isn't it time for a curriculum revision?

Given our current procedural performance, our increasingly busy lives in fellowship, and the reality that most fellows will never or rarely use these skills after graduation, perhaps it would be more valuable to devote that time to learning how to interpret renal imaging or pathology, or focusing on just performing kidney biopsies if desired? At present, the incorporation of imaging and training in kidney biopsy performance appears heterogeneous across fellowships (2). As a result, the command and competency in their use is not equal across the majority of fellows.

Interventional nephrology is a growing subspecialty focused on mastery of the procedural portion of nephrology. The American Society of Diagnostic and Interventional Nephrology (ASDIN) offers resources for nephrologists interested in developing finesse performing procedures (5). The ASDIN requires nephrologists to have completed each procedure as a primary performer a minimum of 25 times to be certified. With these resources available, nephrologists whose jobs require performing procedures can receive the necessary training and certification, just as providers obtain Basic Life Support (BLS) and Advanced Cardiac Life Support (ACLS) certifications when needed.

In the end, while kidney biopsies may still add value for nephrologists in training, temporary hemodialysis catheter placement can be done away with. With the option of getting the necessary certifications for procedures available for those who use them regularly, it is time for the core curriculum to be more in line with current nephrology practices.

Procedures are a core of nephrology

Procedural milestones define the history of nephrology. The first successful dialysis used a rotating-drum kidney with sausage casings. The refinement of shunts made outpatient dialysis a reality. The development of percutaneous biopsies enabled the routine diagnosis and treatment of specific kidney pathologies. Statistics, however, cannot describe why nephrologists in training must hone skills in our "core" procedures.

We provide life-saving dialysis at critical times and must maintain control of how, and when, catheters are placed. Our expertise in placing catheters not only ensures we can provide timely therapy without waiting for other providers, but it helps us understand what patients undergo when a stiff catheter is inserted into their neck or groin. Furthermore, limiting the placement of temporary catheters by other specialties (e.g., our ICU and surgical colleagues) may reduce the number of inappropriately placed or unused catheters. Likewise, as physicians who prescribe risky immunosuppression to fight potentially life-threatening disorders, we must know not just the risks and benefits on paper, but how important trying for a third or fourth pass is.

Relinquishing control over these procedures and reducing our scope of practice may begin a slippery slope toward the elimination of these procedures completely. Indeed, as shown in Figure 1, reducing our procedural experience could further reduce a fellow's confidence and generate greater avoidance of procedures (6). While the ASDIN offers compelling training opportunities, reducing our competencies early on in fellowship may diminish interest in interventional nephrology as a field and thus reduce the number of interventional nephrologists in practice. The loss of procedures may also affect a program's finances by limiting procedural revenue. Last, our current lack of procedures is a factor limiting trainee interest in nephrology (7). Preserving our procedure scope is therefore of paramount importance in ensuring the security of the future nephrology workforce.

Going forward

There is an ongoing debate about which, if any, procedural competencies should continue to be mandated in nephrology training (8,9). Here, we have attempted to highlight views from both sides of this discussion. However, we are of the opinion that if these competencies are to be maintained, our trainees would benefit from the expansion of evidence-based educational modalities (e.g., simulation programs for catheter placement and biopsies) to ensure that we provide quality care throughout the spectrum of nephrology practice.

Arpita Basu, MD, MPH, is a second-year nephrology fellow at University Hospitals-Cleveland Medical Center. Rob Rope, MD, is a third-year nephrology fellow at Stanford University and coordinates the Fellows Corner column for ASN Kidney News.

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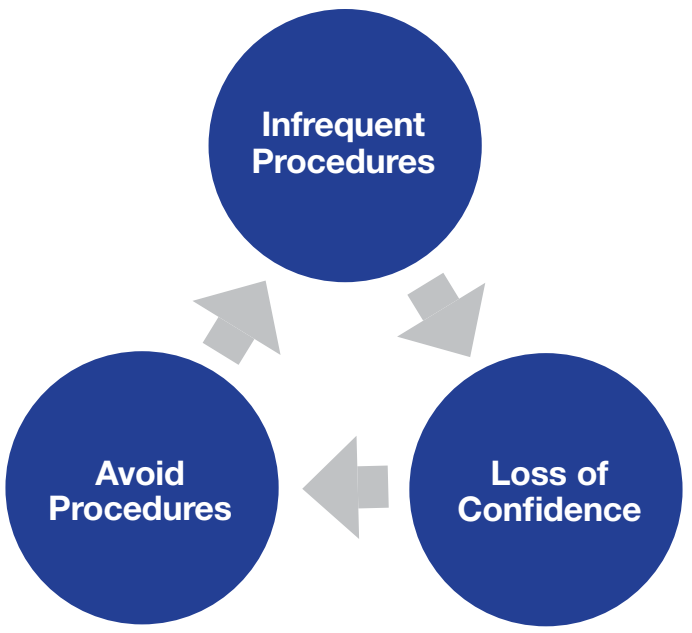
Figure 1. Interplay between frequency and confidence in performing procedures, a vicious cycle whereby performing procedures infrequently leads to loss of confidence, which leads to procedure avoidance.



Courtesy: Mendelssohn DC. Should nephrologists take a larger role in interventional nephrology, and should central line insertion remain a requirement of nephrology residency training? A debate. *Can J kidney Health Dis* 2015; 2:10–12.

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Practice Pointers

Glomerular Disease and Pregnancy

By Jonathan J. Hogan and Melissa Rosenstein

What changes in proteinuria occur during normal pregnancies?

Proteinuria increases over the course of normal pregnancies, in most patients to levels that are still too low to be detectable by urine dipstick alone. Higby et al. (1) analyzed the 24-hour urine collections of 270 healthy pregnant women (<35 years old with no history of preeclampsia, hypertension, pyelonephritis, diabetes, or renal or connective tissue disease) at an average gestation of 26 weeks, finding the mean proteinuria to be 117 mg per day with values at the upper 95% confidence limit to be 260 mg per day. Proteinuria is also increased in twin versus singleton pregnancies, and there is a higher likelihood of developing overt proteinuria (>300 mg/d or urine protein/creatinine [UProt:Cr] ratio of 300 mg/g) in twin pregnancies (2, 3).

How does pregnancy affect patients with preexisting proteinuria?

A few studies have been published describing a significant increase in proteinuria during pregnancy in patients with preexisting proteinuria with diabetes (4) or biopsy-proven, nondiabetic glomerular diseases (5). In one study in patients with diabetes, the mean increase in proteinuria during pregnancy was 248%. This increase in proteinuria may improve or resolve in the months after delivery.

How can one distinguish preeclampsia from other glomerular diseases?

Although performed infrequently, the kidney biopsy remains the gold standard in diagnosing the cause of proteinuria or kidney injury during pregnancy (6). Hypertension is required to make the diagnosis of preeclampsia, but for patients who have underlying hypertensive disease, diagnosing superimposed preeclampsia can be a clinical challenge. Clinical tests (including serum uric acid levels) have not been shown to distinguish preeclampsia from other glomerular diseases in the second and third trimesters. Serum and urine levels of biomarkers, such as soluble fms-like tyrosine kinase 1, soluble endoglin, placental growth factor, and vascular endothelial growth factor, are considered investigational for the prediction and diagnosis of preeclampsia.

Of note, updated recommendations from the American College of Obstetricians and Gynecologists no longer require a 24-hour urine protein collection to make the diagnosis of preeclampsia; a UProt:Cr ratio of 0.3 g/g is sufficient. Also, for the first time, preeclampsia with severe features can be diagnosed in the absence of proteinuria, whereas a serum creatinine of greater than 1.1 mg/dL or doubling of the baseline serum creatinine is now part of the diagnostic criteria (7).

Is it safe to perform kidney biopsies in pregnant patients?

There are limited published data on percutaneous kidney biopsies (PKBs) in pregnant patients. A systematic review of 197 PKBs performed during pregnancy at a median time of 25-week gestation found four patients with major complications (2%), all of which occurred during weeks 23 to 28 (8). All patients developed large perirenal hematomas requiring transfusions. The authors reported one twin pregnancy with an association between kidney biopsy, placental abruption, and preterm delivery, and a second pregnancy where the association between kidney biopsy, preterm labor, and fetal death could not be excluded. Minor complications (hematomas not requiring transfusion and microscopic hematuria with flank pain) occurred in 5% of patients. This study found that a PKB performed for GN or preeclampsia led to changes in management in 66% of patients. Another small study compared PKB complication rates in women with hypertension during pregnancy with those of healthy pregnant controls, with only one major complication observed in a patient with severe preeclampsia (9). A gravid uterus may also necessitate alternatives to the prone position for the biopsy.

Significant renal dysfunction is a contraindication for expectant management of preeclampsia with severe features, and delivery (even at very preterm gestational ages) is recommended. A kidney biopsy is most useful in the early third trimester, because if a nonpreeclampsia diagnosis is made, treatment can be initiated with the goal of prolonging the pregnancy and avoiding the many neonatal complications of prematurity (Table 1). Comparing the risks and benefits of kidney biopsy with delivery should always take into account the gestational age of the fetus and be done in consultation with the obstetrician and neonatologist (10).

What is the effect of preeclampsia on long-term kidney health?

There seems to be a link between the development of hypertensive disorders during pregnancy and kidney disease later in life. One Taiwanese study found an association between hypertensive disorders during pregnancy (including preeclampsia) and eventual chronic kidney disease (adjusted hazard ratio [HR] = 9.38) and ESRD (adjusted HR = 12.4) (11). A second study in Norway showed a low rate of ESRD after pregnancy (3.7 per 100,000 women per year) but that women with preeclampsia had an increased relative risk of ESRD (12). This group also found that women whose pregnancies were complicated by preeclampsia, preterm delivery, and/or intrauterine growth restriction had an increased incidence of requiring kidney biopsies later in life, with a variety of kidney histologies observed. This observation suggests that, in addition to causing direct kidney damage, preeclampsia may also exacerbate or unmask other underlying renal diseases.

It is important to note that the effects of preeclampsia may persist after pregnancy. One prospective cohort study found that it can take as long as 2 years for hypertension and proteinuria to resolve after delivery, with longer time to resolution for patients with more severe hypertension and proteinuria (13).

How does glomerular disease affect pregnancy outcomes and vice versa?

The association between kidney disease and maternal–fetal complications is well-described (14–16), even for patients with preserved GFRs (17). Moreover, patients with moderate and severe renal insufficiency at baseline (generally defined as a serum creatinine <1.4 to 1.5 mg/dL or estimated GFR <40 mL/min) are at risk for developing irreversible worsening of their kidney function during pregnancy, particularly for patients with >1 g per day proteinuria at baseline (18).

Most data on glomerular diseases and pregnancy are descriptive case series from the 1970s to 1990s. However, it is important to recognize these studies' limitations: older or flawed classifications of patients' kidney diseases, conclusions drawn about patients with glomerular disease as a whole rather than by individual disease, and subsequent advances in the understanding and management of these disorders and premature infants. Notwithstanding these limitations, the mere presence of kidney disease has been shown to be associated with adverse maternal and fetal outcomes in multiple studies.

Patients with lupus have significantly higher rates of preeclampsia and other maternal/fetal complications during pregnancy, such as intrauterine growth restriction. A prior history of lupus nephritis is the strongest predictor of these complications as well as development of a lupus flare during pregnancy.

Multiple case series have explored IgA nephropathy and pregnancy, the largest of which are from Japan, China, and Italy. The largest such series (223 women in Italy with IgA nephropathy with serum creatinine <1.2 mg/dL at the time of biopsy) found no difference in the rate of GFR decline in patients who became pregnant versus those who did not become pregnant during the follow-up period (median of 10 years) (19). Other smaller studies have suggested that lower levels of pre-pregnancy proteinuria are associated with improved long-term kidney function and that lower pre-pregnancy GFRs may be associated with higher rates of preeclampsia.

The published literature for patients with minimal

change disease, FSGS, and membranous nephropathy who become pregnant or develop these disorders during pregnancy is limited to case reports and case series.

What medications are safe to use for glomerular disease in pregnancy?

The use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) is contraindicated in the second and third trimesters. There is some controversy about the association between use of ACEIs and ARBs in the first trimester and congenital malformations, but it is currently recommended that they be avoided altogether in pregnancy.

Data quality for the use of immunosuppression during pregnancy is heterogeneous and drawn mostly from the transplant, rheumatology, and oncology literature. Agents used commonly during pregnancy include hydroxychloroquine, glucocorticoids, calcineurin inhibitors, and azathioprine, whereas cyclophosphamide and mycophenolate mofetil are teratogenic and are not recommended. Women using these agents should be asked about their reproductive intentions, and if they desire pregnancy, they should be switched to other agents in the preconception period. Rituximab use during pregnancy has not been found to have an association with congenital abnormalities or miscarriages, although transient depletion of neonatal B cells has been reported (20). It is unfortunate that the letter characterization of the Food and Drug Administration for medication use in pregnancy (categories A, B, C, D, and X) often does not reflect the current clinical practice in using these agents (Table 2). When considering initiating or discontinuing medications for kidney disease, consultation with maternal–fetal medicine specialists is recommended.

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Table 1
Common complications of premature birth

Complication	Treatment(s)
Respiratory distress syndrome	Surfactant, antenatal corticosteroids, respiratory support (CPAP, mechanical ventilation)
Necrotizing enterocolitis	Bowel rest and gastric decompression, antibiotics, surgical intervention if necessary
Intraventricular hemorrhage	Supportive care, neurosurgical intervention if necessary
Hypothermia	Temperature control strategies
Patent ductus arteriosus	Supportive care, closure for severe cases
Hyperglycemia/hypoglycemia	Adjustment of glucose content in feeds, insulin/dextrose infusions as needed
Sepsis	Supportive care, antibiotics
Retinopathy of prematurity	Retinal ablation, anti-VEGF therapy

Abbreviations: CPAP = continuous positive airway pressure ventilation; VEGF = vascular endothelial growth factor

Table 2
Food and Drug Administration pregnancy risk categories for agents commonly used in glomerular disease

Agent	FDA pregnancy risk factor category	Comment
ACEIs, ARBs	D	Contraindicated
Prednisone	C/D	Use permitted during pregnancy, limit dosing
Azathioprine	D	Use permitted during pregnancy
Cyclophosphamide	D	Avoided during pregnancy
Rituximab	C	Limited experience during pregnancy
Cyclosporin, tacrolimus	C	Use permitted during pregnancy
Mycophenolate mofetil	D	Contraindicated; black box warning

Category C: animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Category D: there is positive evidence of human fetal risk on the basis of adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; FDA = Food and Drug Administration.

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ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Industry Spotlight

Research for renal cancer combo drugs picks up

Drug combinations against advanced kidney cancer are the new focus in research and treatment, say many oncology experts. One combination in the news is nivolumab and ipilimumab, each an immunotherapy drug. The first approved (2016) combination for advanced kidney cancer is everolimus plus lenvatinib.

Other combinations, which include some of the aforementioned drugs, are also being tested, in a new era that medical oncologist James Hsieh is calling the Golden Era for advances against kidney cancer.

The types of treatments that are being combined use the properties of vascular endothelial growth factor (VEGF) in drugs that shut down blood supply to tumors (e.g., lenvatinib); of mTOR pathway drugs that block the regulation of cellular metabolism and proliferation (e.g., everolimus); and more recently, of PD-1/PD-L1 immunotherapies that are checkpoint proteins on T cells (e.g., pembrolizumab).

"I see a future where we can take a look at a patient's cancer genomics, figure out what kind of treatment they will benefit from as a frontline, and then we can use a very good combination like VEGF treatment plus PD-1/PD-L1 (antibodies), and I think we should be able to achieve very durable remission for 30% or more of kidney cancer patients," said Hsieh of Sloan-Kettering Memorial Hospital in New York for OncLive.com.

In an interview with TargetedOnc.com, Thomas E. Hutson, DO, PharmD, director of the Genitourinary Oncology Program at the Texas Oncology-Charles A. Sammons Cancer Center Baylor University Medical Center, said of the Study 205 findings on lenvatinib and everolimus that "combination therapy is here to stay for kidney cancer." That trial demonstrated that lenvatinib plus everolimus reduced the risk of progression or death by 63% compared with everolimus alone.

Another example is the combination of immunotherapies nivolumab (brand name Opdivo) and ipilimumab (Yervoy), which is in early-stage clinical trials. The (London) *Independent* newspaper noted: "The results from CheckMate-016 (an early Phase 1 trial) are encouraging, and warrant further study, as they show with nearly two years of follow-up, 40.4% of patients in each nivolumab plus ipilimumab combination arm responded to the regimen, with the majority of responses occurring early and within the first few months of treatment," quoting Hans Hammers, MD, a kidney cancer specialist from the University of Texas Southwestern Medical Center in Dallas.

"There remains a significant unmet need for treatment options that offer ongoing responses and increase survival for patients with renal cell carcinoma," Hammer said.

Baylor's Hutson noted that at the 2016 European Society of Medical Oncology Congress there was news of a variety of combinations that will be employed. "With combination therapy, there is the toxicity concern that we will need to make judgments about," he said. "People often bring up cost of care when we bring up combination therapy. That is something that we, as a society, are going to have to address."

He noted that another combination trial is in a Phase 3 study. It will be a three-arm study comparing lenvatinib (Lenvima) plus everolimus (Afinitor), versus lenvatinib and pembroizumab (Keytruda), versus a single drug, sunitinib (Sutent).

Another drug, cabozantinib (Cabometyx), is in a Phase 1b combination trial with immunotherapies through work with manufacturer Exelixis' collaborators at the National Cancer Institute, according to the company. The trial will explore cabozantinib in combination with nivolumab alone, or in combination with nivolumab plus ipilimumab, in patients with genitourinary tumors, including renal cell carcinoma.

FDA approval for Parsabiv

After a rejection last year by the U.S. Food and Drug Administration (FDA) and the need for a complete response letter explaining data, Amgen (Thousand Oaks, CA) now has gained FDA approval for its drug Parsabiv. Approved in early February, the drug treats secondary hyperparathyroidism (secondary HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

Parsabiv is the first therapy approved for this condition in 12 years and the only calcimimetic drug that can be administered intravenously by the dialysis health care team three times a week at the end of the hemodialysis session, Amgen stated.

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.

The drug mimics the action of calcium by activating calcium-sensing receptors on the parathyroid gland, which in turn decreases levels of parathyroid hormone, reports Thomson Reuters news agency. Annual sales of the drug are forecast to exceed $600 million by 2023.

Vascular Access and Self-Care Opportunities

More control over vascular access in dialysis can be an important part of dialysis self-care.

In addition to dialysis centers training patients to handle their own vascular access when motivated to learn, a new maker of venous access, Advent Access (Singapore), is positioning itself as a "disruptive" new technology that will further help patients on dialysis.

Advent Access's "device-guided blunt access" proprietary platform aims to preserve AV fistula health and potentially allow hemodialysis centers to treat a larger patient population with fewer nurses or other support. The company's subcutaneous access device is placed adjacent—but noninvasive— to an AV fistula.

When asked how Advent Access would disrupt current dialysis customs, founder Peh Ruey Feng in Singapore said, "We want to maintain the health of the AV fistula vein, preventing operator-related complications in the first place," he told the (Singapore) *Straits-Times* newspaper. Reh said self-care among dialysis patients is possible, although the Achilles heel of self-hemodialysis has been managing vascular access.

Dialysis care providers like Diaverum (Munich, Germany; formerly Gambro) offer several steps of self-care and related training in their centers, including preparing equipment and supplies, placing the needle in the vascular access site, administering medication, monitoring the machine, and record-keeping.

DaVita noted that its patients and their caregivers can also learn and be trained to perform self-care tasks from washing the access site during care to self-cannulation.

Outset Medical's (San Jose, CA) Tablo system is a standalone full-service dialysis unit that produces dialysate with tap water, rather than a central water treatment room, and completes blood processing. Patients can hook themselves up to the machine in about 10 minutes and as quickly as six minutes, according to Outset CEO Leslie Trigg.

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CMS deadline for Medicare EHR attestation is March 13, 2017

The deadline for filing a meaningful use report with the Centers for Medicare & Medicaid Services (CMS) fast approaches. If providers wish to continue participating in the Medicare EHR (Electronic Health Record) Incentive Program, they must let CMS know by 11:59 pm March 13.

The Medicare EHR Incentive Program pays an incentive to Eligible Providers (EPs) who can attest that they are "meaningfully using" their certified EHRs by meeting thresholds for 10 specific objectives (e.g., using computerized provider order entry, and generating and transmitting permissible prescriptions electronically).

According to CMS, the following individuals are considered EPs who may participate in the EHR Medicare Incentive Program: doctors of medicine or osteopathy, doctors of dental surgery or dental medicine, doctors of podiatry, doctors of optometry, and chiropractors. Hospitals and critical access hospitals may also participate in the Medicare and Medicaid EHR Incentive Programs through 2017 and beyond.

Beginning on a voluntary basis in 2017, and on a required basis in 2018, all providers will attest to Stage 3 objectives and measures, which include demonstrating advanced clinical processes and showing improved outcomes. EPs must achieve defined objectives in order to receive incentive payments.

Beginning in 2015, eligible professionals who did not successfully demonstrate meaningful use were subject to a payment adjustment. The payment reduction starts at 1% and increases each year that an eligible professional does not demonstrate meaningful use, to a maximum of 5%.

The Medicaid EHR Incentive Program

CMS offers two EHR incentive programs, one for Medicare and one for Medicaid. EPs can only participate in one of the programs. If an EP chooses to participate in the Medicaid EHR Incentive Program, she or he can participate in only one state's incentive program in any given year.

There are no Medicaid payment reductions for eligible providers who choose not to participate.

EPs in their first year of Medicaid EHR incentive participation will have to demonstrate that they were able to "adopt, implement, or upgrade their certified EHR system," according to CMS. The second year and thereafter, they will have to attest that they meet the meaningful use requirements and all other eligibility criteria. EPs in the Medicaid EHR Incentive Program need to meet the same 10 objectives as those participating in the Medicare counterpart program.

The Medicaid EHR Incentive Program includes physicians (MDs and DOs), nurse practitioners, certified nurse-midwives, dentists, and physician assistants who lead a federally qualified or rural health clinic.

The Medicaid EHR Incentive program deadlines are different for each state. Please check https://www.cms.gov/apps/files/statecontacts.pdf to find state deadlines.

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