activity independent of age (which was matched in this study) and comorbid conditions (which were absent).

Another important finding was that animals with CKD and access to a wheel were more active than those without access, although they were not compelled or incentivized to be more active. Obviously, the human environment is less easily controlled, and human motivations are complex, but this result suggests that providing access to physical activity is likely to increase it, even in the setting of CKD. Finally, wheel running improved serum creatinine concentration, cystic kidney weight, serum phosphorus, and parathyroid hormone in the rats with CKD, and it also increased muscle strength and exercise capacity. Thus, exercise slowed the progression of kidney disease, lessened manifestations of CKD-related mineral and bone disorder, and improved physical function, benefits that investigators have hypothesized might accrue to patients but have had difficulty studying.

How can we apply these results to patients with CKD? Although the intensity of exercise could not be precisely quantified in this study, it seems to have been moderate. Contrasting these results with those of the investigators’ prior work, in which forced, high-intensity treadmill exercise actually led to negative results, may be instructive. Overtraining may be an important consideration among animals and patients with CKD who have very low exercise capacity at baseline. Difficulty recruiting patients for exercise studies and high rates of dropout of enrolled participants could reflect patients’ fear of or actual negative experience with vigorous training.

The results of this study by Avin et al. serve as an exciting demonstration of the potential benefits of moderate-intensity exercise among patients with CKD. They align with a key message from the new 2018 physical activity guidelines for Americans that the greatest health benefits accrue by moving from no to even small amounts of physical activity. In a recent pilot study, patients on dialysis who were advised to walk more but allowed to determine the speed and timing of walking increased their activity, analogous to the rats’ volitional wheel running in the study by Avin et al. Larger studies of lower-intensity exercise requiring fewer resources and powered to examine important outcomes are urgently needed in the CKD and ESKD populations.

DISCLOSURES

Dr. Johansen is a member of the Steering Committee for GSK’s ASCEND study program.

REFERENCES


Transplantation of Kidneys from HCV Viremic Donors in the United States: A Missed Opportunity to Inform Clinical Decision Making and Health Policy

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In this issue of JASN, Potluri and colleagues report a marked increase in the availability and use of kidneys from HCV viremic deceased donors for transplantation as a result of the opioid epidemic and the advent of direct-acting antivirals (DAAs). Historically, transplantation of these kidneys was restricted to HCV-positive waitlist candidates and most were either not retrieved or discarded. DAAs now allow...
consideration of using kidneys from HCV viremic donors in both HCV-positive and HCV-negative waitlist candidates.

The study used national data collected by the Organ Procurement and Transplant Network (OPTN) between December 2015 and March 2019 and reported a nearly six-fold increase in the number of waitlist candidates willing to accept a kidney from a donor with any evidence of HCV infection, including a doubling of patients willing to accept a HCV viremic donor kidney. As a result, transplantation of kidneys from HCV viremic donors in HCV-negative patients now outpaces their use in HCV-positive patients. Although the nonuse of kidneys from HCV viremic donors remained higher than that of kidneys from HCV seronegative donors, discard rates declined and fewer kidneys with otherwise favorable donor characteristics were discarded. Of note, the utilization of such kidneys varied geographically and in several regions there were no transplants involving HCV viremic donors in HCV-negative recipients. This variation in part reflects the geography of the opioid epidemic, but also indicates variation in acceptance of viremic kidneys by the transplant community.

The increased acceptance and utilization occurred despite limited information about the long-term safety and efficacy of DAAs in the transplant setting, especially in facilitating transplantation for HCV-negative patients. The potential to use kidneys from HCV viremic donors in HCV-negative patients was demonstrated in two small studies involving a total only 20 patients.2,3 Both studies reported sustained viral remission after DAA treatment but did not report long-term outcomes.

In contrast to the robust information regarding kidney utilization, this study provides limited information about the long-term safety of such transplants. The outcomes of 103 HCV-negative recipients of an HCV viremic donor kidney with at least 12 months of available follow-up, were compared with those among a rigorously matched cohort of recipients of HCV nonviremic donor kidneys. The authors found no difference in patient or allograft survival, and no difference in eGFR or reported acute rejection events. The eGFR of transplants using HCV viremic donors was similar in patients with and without serological evidence of HCV infection, suggesting that recipient serostatus does not affect the function of transplants from HCV viremic donors.

The promising short-term outcomes led the authors to challenge the continued inclusion of HCV donor infection in the calculation of the Kidney Donor Profile Index, an equation that predicts the risk of allograft failure that is used to determine the allocation of deceased donor kidneys. The authors believe that donor HCV status no longer represent a negative prognostic factor for transplant failure in the era of DAAs. Given the absence of information about long-term patient and allograft survival, and the likely careful selection of HCV-negative recipients, it is premature to alter established allocation policy on the basis of this report.

Although the study provides important information to support the continued transplantation of kidneys from viremic donors in recipients with and without preexisting HCV infection, many critical questions, including the timing, duration, efficacy, and complications of DAA use in the transplant setting remain that cannot be addressed because of the limitations of OPTN data. Information regarding the donor HCV genotype, viral load, presence and effect of DAA resistance–associated substitutions, patient selection criteria, DAA and immunosuppressant regimens, and major complications including fibrosing cholestatic hepatitis is critical to inform the expanded use of kidneys from HCV viremic donors that the authors advocate for. Although requirements for additional data collection are often met with resistance, this information could have been added at minimal cost to the OPTN.

The study also raises new questions regarding the optimal allocation of HCV viremic kidneys. Specifically, should these kidneys be preferentially allocated to patients with preexisting HCV infection to minimize the overall health care costs of DAA treatment? Related to this issue is the optimal timing of transplant of HCV-positive waitlisted transplant candidates. Because of the increased utilization of HCV viremic kidneys in HCV-negative candidates, existing recommendations to defer HCV treatment in clinically stable HCV-positive candidates until after transplantation may warrant reconsideration if this approach fails to provide these patients with more rapid access to transplantation from a viremic donor. Given the large geographic variation in the utilization of HCV donors, such management decisions may vary between regions. This issue will also not be fully informed without additional data collection. Because HCV status is currently not collected at time of waitlisting, the timing of transplantation in HCV-positive candidates with a kidney from a donor with or without viremia may be difficult to predict.

The current uncoordinated approach to HCV transplantation in the United States provides an opportunity to reflect on the strengths and weaknesses of the transplant system. Recognizing the potential to significantly increase the supply of deceased donor kidneys in the DAA era, the American Society of Transplantation (AST) provided recommendations for the transplantation of organs from HCV-infected donors.4 The ability to rapidly bring together experts and key stakeholders to inform best practice is a strength of the transplant community. Unfortunately, the recommendations did not lead to a coordinated collaborative approach for using HCV-infected donor organs. The current report is unable to determine how many transplants involving HCV viremic donors in HCV-negative recipients were performed in an institutional review board approved study as recommended by the AST. In the absence of a government-funded multicenter study, as mandated by the HIV Organ Policy Equity Act of 2013 for the use of organs from HIV-infected donors, or an industry partner, the community lacks mechanisms for centers to collaborate to test innovative therapies (such as DAAs) in the real-world setting. Such collaborations should be enabled by the existence of a world leading transplant registry. To date, the OPTN registry has been underutilized to advance clinical...
innovations and this functionality should be developed. The report of Potluri and colleagues reveals the depth of patient trust in their care providers to provide them with best evidence-based advice regarding their transplant options. It is our responsibility to ensure we maximize the information obtained from their experience to better inform decision making for future patients.

DISCLOSURES

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REFERENCES


Machine Learning Comes to Nephrology

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Nephrology has been affected for decades by advances in technology: from Western blotting and reporter gene assays to multiphoton imaging and next-generation sequencing.

Initially exotic techniques eventually find their way into nephrology’s DNA.

Among the latest exotic technologies affecting nephrology is machine learning (ML). Just one manifestation of artificial intelligence, ML is a collection of computationally intensive statistical learning techniques. It is the result of the challenge of big and high-dimensional data and the development of the hardware (graphical processing units, mass digital memory storage) and software needed to understand it. The rapid expansion of whole slide imaging by digital slide scanners has provided fertile ground for ML in renal pathology. Rather than trying to build in hardcoded models on the basis of prior knowledge and rules to predict outcomes, ML allows a program to learn from experience alone, improving its performance iteratively on a training set by comparing its predictions to authoritatively labeled cases (ground truth) and adjusting a very large number of weighting parameters in the model so as to minimize a loss function, which represents the distance between prediction and truth. This characterizes supervised learning. This process of parameter adjustment is iterated many dozens of times to “train” the model. Each complete passage of training data through the model (an epoch) may require many millions of calculations. Optimization (fine-tuning) of the hyperparameters (such as learning rate, depth of the model, and number of epochs), which determine the overall architecture of the model, is performed on a separate validation set, typically 20% of all the training data. Finally, the model is tested on annotated data that was held out from the training and validation sets. If this is not feasible because of the small number of cases, other options include k-fold crossvalidation and using bagged (bootstrap aggregated) data.

Uses of ML in nephrology include predicting AKI or time to allograft loss from clinical features, recognizing specific histologic features in a biopsy, choosing an optimal dialysis prescription, or mining text in the electronic health record to find specific cases. Unsupervised learning methods, less often applied in biomedicine, recognize clusters of unlabeled individuals by their proximity in some multidimensional feature space. These methods are typically used to reduce data dimensionality, cluster data or detect patterns, and find outliers.

One of the most often used ML architectures is a convolutional neural network (CNN), a type of artificial neural network that underlies “deep learning.” This powerful tool was used in two papers published in this issue of JASN. The workings of a CNN can be reasonably well explained by a familiar biologic system. In analogy to the mammalian visual system, a multilayered system of interconnecting neurons converts the primitive events of retinal photoreception (corresponding to pixels of an image) to the activation of the proverbial “grandmother” cell in the visual cortex, the final integrating neuron that fires only when the retina is exposed to grandma’s image, as a form of recognition or classification. The “hidden layers” between the visible input and output layers consist of layers of neurons wherein activation of a