A Change in Praxis: Making the Most of Each Donated Kidney

By Abhinav Bhalla and Darshana M. Dadhania

Despite more than 90,000 patients waitlisted for a kidney transplant, 21.3% of donated kidneys were not used according to the 2020 Annual Data Report of the Scientific Registry of Transplant Recipients and Organ Procurement and Transplant Network (1). As organ demand far exceeds supply, transplant professionals strive to break barriers and improve utilization of available kidneys (2, 3). Seminal studies, such as Transplanting Hepatitis C Kidneys into Negative Kidney Recipients (THINKER) (4) and Exploring Renal Transplants Using Hepatitis C Infected Donors for HCV-Negative Recipients (EXPANDER) (5), have transformed the way we use kidneys from donors who are hepatitis C virus (HCV) positive. The combination of novel direct-acting antiviral (DAA) therapies for HCV, with cure rates approaching 100% (6), and the unfortunate rise in opioid overdose-related mortality of young individuals (7) has translated into an unanticipated opportunity for those with chronic kidney disease (CKD) who are waitlisted for a kidney transplant (8). The dramatic change in praxis as it relates to utilization of HCV-positive kidneys for transplantation is shown in Figure 1A.

In the article entitled "Kidney transplantation from hepatitis C virus-infected donors to uninfected recipients: A systematic review for the KDIGO [Kidney Disease: Improving Global Outcomes] 2022 hepatitis C clinical practice guideline update" by Gordon and colleagues (9), the authors performed a systematic review on the use of donors who are HCV viremic for kidney transplantation into recipients who are HCV naïve (donor [D]+/recipient [R]−). Sixteen investigations of HCV D+/R− kidney transplantation, comprising 557 patients, were evaluated using a specified protocol for DAAs. Sustained viral response at 12 weeks was reported in all studies and was achieved in 97.7% of patients (95% confidence interval [CI], 96.3%−98.8%). Although a shorter course of DAAs resulted in high rates of viremia, those who remained viremic after the initial treatment achieved viral clearance following retreatment. Serious adverse events were reported in 69% of the studies and were uncommon at a rate of 0.4% (95% CI, 0.1%−2.8%). Three cases of fibrosing cholestatic hepatitis were reported among 211 patients, two with a delayed start of DAA therapy; all three had complete resolution.

The mortality at 1-plus year was 2.1%, and the data appeared to be similar to the outcome in HCV D−/R− transplants. One-year kidney graft survival was 97.6%, similar to HCV D−/R− transplants. These data support the recently published 2022 KDIGO guidelines on management of HCV in CKD, which strongly recommend consideration of hepatitis C-positive kidneys for all recipients irrespective of their serological status (10).

Although the results are promising, the authors caution about the lack of long-term data on the safety and graft survival in HCV D+/R− transplants. In this publication, HCV-positive kidneys were associated with 51% lower rates of delayed graft function compared with HCV D−/R−, and there was no difference in the acute rejection rates. It remains to be seen if this translates into a better long-term graft survival for HCV D+/R− transplants. Given these data, the cost of DAA therapy for HCV seems like a small price to pay for the savings gained by transitioning a patient off of dialysis to a functioning kidney allograft.

With the increase in kidney donors who are HCV positive, the transplant community will need to ensure that there is equal access to these organs. Prompt review of data and development of practice guidelines such as the KDIGO 2022 Hepatitis C Clinical Practice Guideline will facilitate education and adoption of these novel approaches by practitioners (10). Equally important are the goals of educating our patients and ensuring insurance coverage for the much-needed DAA therapies that cost more than $84,000 for a 12-week treatment (11). As noted by Gordon et al. (9), some patients did experience fibrosing cholestatic hepatitis when there was a delay in DAA therapy.

Since the gap between supply and need for kidneys remains large, it is imperative that innovative protocols are established to reduce kidney discards and optimize the long-term success of kidney transplants. Publication of the EXPANDER (5) and THINKER (4) trials in 2018 laid the foundation for transplantation of >7500 kidneys from donors who were HCV positive. The proportion of HCV-positive kidneys transplanted into recipients who are HCV negative has increased from 5% in 2015 to >90% in 2022 (Figure 1B). The systematic review by Gordon et al. (9) should further educate the transplant community and facilitate optimal utilization of the donor pool. ■

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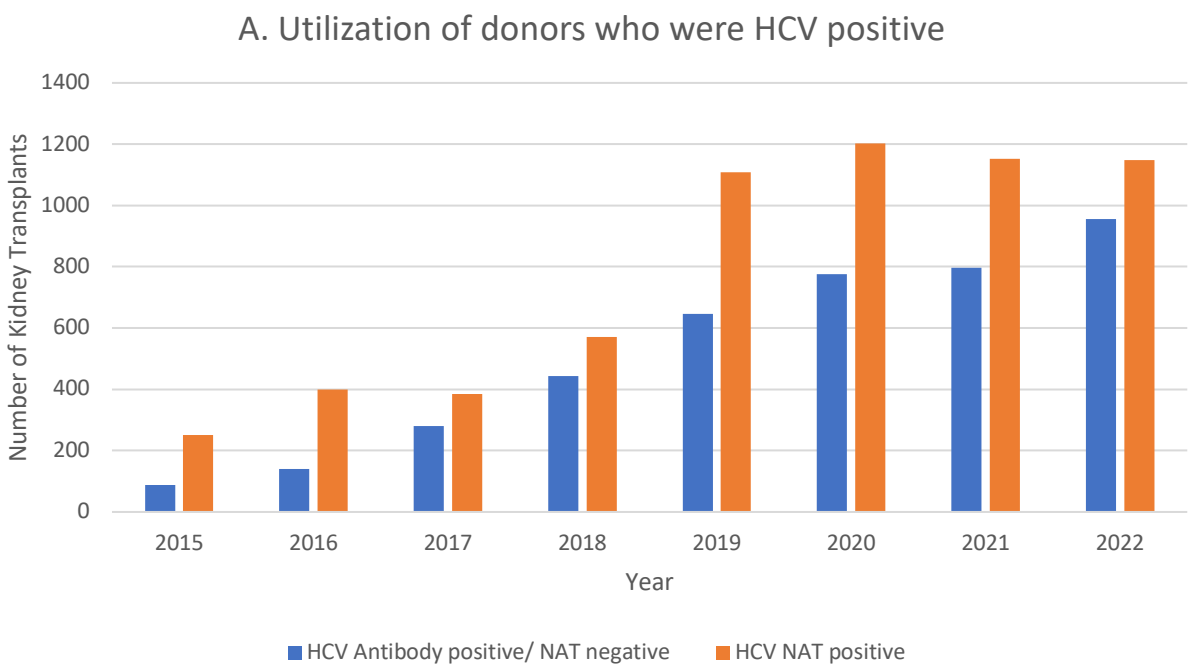
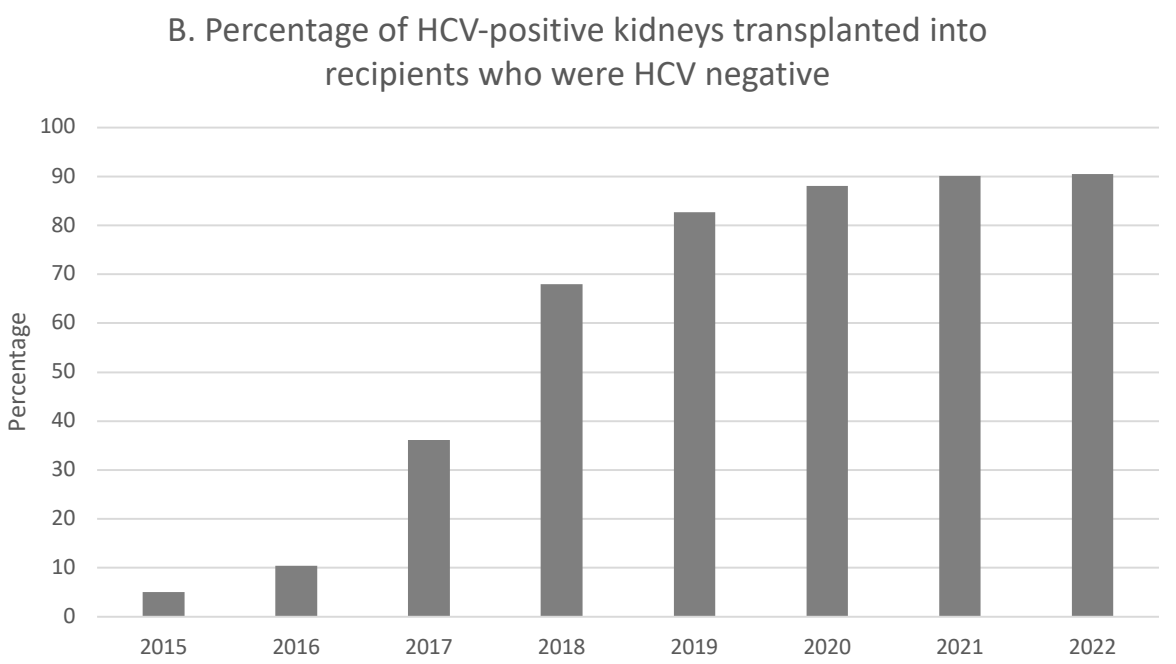
Figure 1. Transplantation of HCV-positive kidneys





Data are based on deceased donor kidney transplants performed in the United States between April 1, 2015, and December 31, 2022, provided by the Organ Procurement and Transplantation Network on May 10, 2023. NAT, nucleic acid test.

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Decoding IgG4-Related Kidney Disease: Unlocking Clinical Insights and Prognostic Clues

By Jacob Nysather and Prakash Gudsoorkar

Immunoglobulin G4 (IgG4)-related disease is a systemic, fibro-inflammatory disorder with pseudotumoral lesions, IgG4-positive lymphoplasmacytic infiltrates, and tissue fibrosis that can be seen within any organ (1). Serum IgG and IgG4 levels are typically elevated, but normal levels do not rule out the diagnosis. Kidney involvement occurs in 30% of cases, presenting as tubulointerstitial nephritis, glomerular lesions (e.g., membranous nephropathy), and macroscopic kidney abnormalities (bilateral kidney hypertrophy, pseudotumors, and hypermetabolic kidney lesions on 18-F-fluorodeoxyglucose-positron emission tomography-computed tomography [18-FDG-PET-CT]).

A retrospective, observational cohort study by Anis Chaba et al. (2) analyzed 101 adult patients from 35 European sites with IgG4-related kidney disease from January 1997 through December 2019. Patients were categorized into two groups: 1) kidney involvement without an alternative diagnosis and 2) established IgG4-related disease with kidney failure, proteinuria, and/or kidney lesions on imaging. Exclusions were retroperitoneal fibrosis and incomplete follow-up. Data on clinical, biological, imaging, and histopathological features; treatment; and outcomes were collected.

Kidney involvement was seen in 60% of patients, and 86% had systemic involvement at diagnosis. Extrarenal features included lymphadenopathies (57%), autoimmune pancreatitis (42%), sialadenitis (36%), lung involvement (28%), and cholangitis (25%). Laboratory findings revealed hypergammaglobulinemia, elevated IgG4 levels (94%), and decreased complement (C) levels (45%).

Among the patients, 51% had acute kidney injury (AKI), 23% had AKI-on-chronic kidney disease (CKD), and 14% had isolated CKD. Median serum creatinine (sCr) was 2.4 mg/dL (interquartile range [IQR], 1.6–3.6) with a corresponding estimated glomerular filtration rate (eGFR) of 25 mL/min/1.73 m² (IQR, 17–43). Primary urinalysis findings were often without active sediment; however, hematuria and leukocyturia were noted in 27% and 16%, respectively. The median urinary protein-to-creatinine ratio was 600 mg/g (IQR, 200–1100), with >1000 mg/g in 31% of cases, primarily indicating glomerular involvement. CT scan abnormalities were found in 61% of patients, including bilateral kidney hypertrophy, pseudotumor, and low-density areas. An 18-FDG-PET CT scan was performed in 63% of patients, revealing hypermetabolic kidney lesions in 38% and extrarenal lesions in 74%.

Kidney biopsies were conducted in 82% of patients, showing tubulointerstitial involvement in all cases and additional glomerular lesions, most commonly membranous nephropathy, in 16% of cases. Tubulointerstitial lymphoplasmacytic infiltrates and predominant IgG4(+) plasma cells were observed. Dense fibrosis (>50% kidney tissue) was described in 42% of cases, whereas the storiform pattern was rare.

Corticosteroid (CS) therapy was administered to 90% of patients (mean dose, 0.8 ± 0.3 mg/kg/day), and 18 patients (18%) received rituximab as initial therapy (77% received 1 g at days 1 and 15, around two cycles). No specifications were made on which patients received chosen therapies. After a median follow-up of 24 months, 35% of patients experienced relapse, with a median relapse time of 12 months. Multivariable analysis showed that muti-organ involvement and low C3/C4 levels were associated with a higher relapse risk, whereas rituximab was associated with a lower risk. This effect persisted after weighting and propensity score analysis.

Patients who received rituximab first had lower relapse rates (22% vs. 37%) and similar kidney outcomes with lower rates of complications such as death (6% vs. 15%) and infections (17% vs. 25%). At the last follow-up, 71% of patients had CKD, with a median eGFR of 45 mL/min/1.73 m², and 32% had an eGFR ≤30 mL/min/1.73 m². Progression to end stage kidney disease occurred in 12% of patients, and 13% died. Factors associated with severe CKD were age, peak sCr, prolonged CS duration (>12 months), and cholangitis. Logistic regression analysis identified age, peak sCr, and serum IgG4 levels ≥5 g/L as independent predictors of severe CKD. Serum IgG4 levels at diagnosis and the state of interstitial fibrosis and tubular atrophy on kidney biopsy were related to eGFR at the last follow-up.

This retrospective analysis highlights IgG4-related kidney disease primarily affecting middle-aged males and presenting as tubulointerstitial nephritis with glomerular involvement in approximately 25% of cases. CSs are commonly used but carry a relapse risk, especially in patients with CKD. Rituximab shows promise as a first-line treatment to reduce relapse rates. Close monitoring is essential for individuals with organ involvement and elevated IgG4 levels, as these conditions are associated with poorer outcomes. Given the 23 years examined within this retrospective study, it is difficult to compare cases, particularly with advancements in biomarkers and therapeutics. Further controlled trials are needed to confirm these findings. ■

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