

need for interventions and their effect on AVF patency and future interventions. Studies are required to not only help predict which patients will likely have AVFs that will mature but also, those that will require procedures to assist maturation and patency. There is currently a paucity of validated algorithms to help select vascular access, and prior prediction tools for AVFs that fail to mature are outdated. The energy, resources, and educational efforts put into the original nationwide Fistula First initiative were highly successful in moving the needle to create more AVFs. We now need to revitalize research in vascular access and redirect our energies, efforts, and resources to updating and educating nephrologists, interventionalists, surgeons, dialysis staff, and associated trainees on how to properly assess and individualize approaches to vascular access choice and appropriate management. The goal remains unchanged: to help each patient attain a reliable dialysis access that can provide the prescribed dialysis for each patient's individual circumstances with as few complications and interventions as possible.¹⁷

DISCLOSURES

None.

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See related article, "Long-Term Outcomes of Arteriovenous Fistulas with Unassisted versus Assisted Maturation: A Retrospective National Hemodialysis Cohort Study," on pages 2209–2218.

Tracking HLA Antibody Changes among Kidney Waitlist Candidates: One Protocol May Not Fit All

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Kidney transplantation remains the treatment of choice for ESRD; however, in the absence of a compatible living donor, patients may wait years or decades for a transplant opportunity.^{1,2} HLA sensitization can prolong a candidate's waiting time even further by reducing donor offers to only those

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with compatible HLA mismatches. Currently, the composition of most kidney waiting lists includes >35% sensitized candidates and, in the United States, the breadth of HLA sensitization among sensitized candidates is evenly dispersed between low (calculated panel reactive antibody [CPRA] 1%–19%), moderate (CPRA 20%–79%), and high (CPRA >80%) categories. Sharing of donor organs across larger geographic regions increases the donor pool size and the likelihood of finding a compatible donor for sensitized candidates.^{3,4} Furthermore, providing additional allocation points according to HLA sensitization breadth ensures that these compatible donors are offered first to sensitized candidates.^{2–4} These strategies have increased transplant rates for sensitized candidates in the United States and Europe with the goal of providing greater equity among candidates and reducing waiting list mortality.

Successful execution of these complex allocation algorithms relies on accurately matching candidates with the appropriate donor organ in a time-efficient manner. Thus, transplant centers must develop sustainable protocols for screening and managing growing waiting lists so that each candidate is medically ready and eligible to accept the optimal donor offer. Managing sensitized waiting list candidates requires regular serum screening to monitor changes in HLA antibody breadth and strength. When waitlist candidates are exposed to foreign HLAs through pregnancy or transfusion, this can initiate or broaden HLA sensitization.^{5,6} In presensitized candidates, HLA antibody breadth and strength can also change in response to inflammatory events such as infections, surgical procedures, or vaccines.^{7,8} Thus, HLA sensitization is dynamic and adequate monitoring is crucial for ensuring compatibility when a donor organ for a sensitized candidate is finally identified.

Transplant centers differ in their algorithms for test frequency and initiation of HLA antibody screening to maintain cost effectiveness. Regions with longer wait times may activate a candidate on the waitlist, but not begin screening for HLA antibodies until they have accumulated sufficient waiting time to receive donor offers. Other centers may determine testing frequency by the candidate's sensitization status and still others may use a one-size-fits-all algorithm testing all candidates with the same frequency. There are few studies examining optimal waitlist management and no published data examining whether the common practice of monitoring HLA antibodies at quarterly intervals is most effective. Although growing a center's waiting list may facilitate higher transplant numbers, it must be balanced with the cost and effort of managing large waiting lists given the proportion of candidates who are HLA sensitized and/or medically complex due to comorbidities associated with ESRD.

In this issue of *JASN*, Togninalli *et al.*⁹ examine HLA class I and class II antibody levels for 627 candidates on the University Hospital Zurich deceased donor kidney waiting list. The goal of their study was to investigate the kinetics of HLA antibodies over time, as measured by median fluorescence

intensity (MFI) on a single antigen bead assay, in an effort to find the optimal time interval between testing to improve the accuracy and efficacy of monitoring protocols. They examined changes in MFI between consecutive measurements for individual patients and tracked this in relation to the time interval between measurements. Surprisingly, the authors found no correlation between mean MFI change and the time interval between testing (range, 3–12 months). Next, they examined the effect of testing frequency on the ability to detect HLA antibody changes relative to published clinical thresholds used for HLA antibody detection and unacceptable HLA antigen assignment (1000 and 5000 MFI), but were still unable to pinpoint an optimal screening frequency. Nevertheless, the data did reveal differences in HLA antibody kinetics among candidates stratified by the route of HLA alloimmune exposure. Candidates with previous transplants showed greater fluctuations in their HLA antibody levels compared with candidates with a history of pregnancy or transfusions. This finding correlates with other studies showing that HLA sensitization stemming from failed transplants elicits stronger and broader HLA antibody levels and a higher prevalence of HLA-specific B memory cells that can be reactivated during times of inflammation.¹⁰ The study was unable to cluster candidates on the basis of statistical properties related to the HLA antibody kinetics, thus illuminating the high degree of complexity and individual variability in HLA-directed humoral responses.

Although the findings of this study are enlightening, a number of limitations within the available dataset prevented detailed guidance for optimizing the screening of sensitized waitlist candidates. Protocol testing data were not available to examine HLA antibody variability within a ≤ 30 -day testing interval. Many centers follow a quarterly monitoring protocol, but require a serum drawn within 30 days for crossmatch assessments to determine final transplant eligibility. Determining the optimal testing interval for candidates with the greatest HLA antibody variability is essential for facilitating efficient kidney allocation across greater distances with fewer unexpected crossmatch results. Commonly used tools such as CPRA or calculated reaction frequency (cRF), which reflect the breadth of HLA sensitization as it relates to deceased donor HLA haplotype frequencies, were not available to inform whether a certain threshold of CPRA results in greater HLA antibody fluctuation, independent of mode of sensitization. Given that rejection of a previous allograft and removal from immunosuppression likely elicit the strongest alloimmune response, candidates with previous transplants in this study may also possess higher CPRAs. Therefore, it is unclear whether stratification by CPRA alone may identify female candidates sensitized *via* pregnancy that also show complex HLA antibody kinetics. Furthermore, the study was not able to examine the specific clinical events associated with changes in HLA antibody levels such as hospitalizations, infections, or vaccinations, or the optimal timing of testing after these clinical events.

Overall, this study advocates for a stratified protocol for HLA antibody screening and highlights the importance of

obtaining detailed medical histories surrounding allosensitization and proinflammatory events at time of listing, while maintaining candidates on the waiting list, and at the time of transplantation. These points are important and timely given that centers are moving away from “real-time” crossmatch testing at time of donor offer and toward virtual crossmatch assessments that use retrospective HLA antibody testing data.

DISCLOSURES

Dr. Jackson serves on a Speaker Bureau for One Lambda, Thermo Fisher and as a scientific consultant for Hansa Biopharma. Dr. Manook has no conflicts of interest to disclose.

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