

American Society of Nephrology – Comments
Centers for Medicare & Medicaid Services
Medical Evidence Development and Coverage Advisory Committee (MedCAC) meeting
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January 19, 2011

Since the first successful kidney transplant was performed in 1954 hundreds of thousands of patients with fatal end-stage renal disease (ESRD) have received the Gift of Life and have gone on to live productive and almost normal lives for many decades. Over the years, the outcomes of kidney transplantation have improved dramatically due to improvements in immunosuppression, donor selection, surgical techniques, improvements in infectious prophylaxis and so forth. Currently, one-year patient and graft survival rates are more than 95% and acute rejection rates are one-fifth of what they were two decades ago. There is no doubt that kidney transplantation is the preferred treatment for ESRD and provides substantial benefits over chronic dialysis. In 1984 the United States Congress passed the National Organ Transplant Act (NOTA) which established principles for allocation of deceased donor organs for transplantation and provided other structures for the transplant community. Importantly, NOTA established the Organ Procurement and Transplant Network (OPTN) one of whose functions is to maintain a registry of all human organ transplant procedures performed in the United States. In addition, NOTA further established the Scientific Registry of Transplant Recipients (SRTR) which is responsible for analyzing the data submitted to the OPTN by the transplant centers. This registry and its analysis are freely available on the organizations' web sites (www.optn.org) and www.ustransplant.org). Importantly, the registry is a universal database containing information about every donor and recipient of organ transplants for the past 23 years. With appropriate analysis, the registry provides comprehensive and accurate information about risks for patient outcomes and graft survival, risks for rejection, center specific results, and so forth.

Unfortunately, organ transplantation is not available for every patient with ESRD. There currently are more than 300,000 patients with ESRD being treated with chronic dialysis in the United States. Of these, 80,000 are awaiting kidney transplantation. Last year, there were only 15,000 transplants performed in the United States, approximately 10,000 from deceased donors and about 5,000 from living donors. The number of transplants performed is limited by the number of available organ donors, not by the number of patients who could benefit from the procedure.

A major impediment to the success of kidney transplantation is the human immune response to foreign antigens. Clearly, classic acute rejection is the result of cell-mediated mechanisms. However, antibodies against human leukocyte antigens (HLA) also can mediate both immediate and indolent destructive immune responses. In general, humans develop antibodies to HLA antigens by being exposed to antigens from other individuals. The three principal mechanisms by which patients develop these antibodies, which is known as "sensitization", are through blood transfusions, having received a prior organ transplant, and by having been pregnant. There have been reports of broad-based sensitization resulting from exposure to de-vitalized tissues such as tendon transplants and cardiovascular valves and conduits, but the three methods listed above are considered the primary sensitizing events.

Before the introduction of erythropoietin (ESA) dialysis patients routinely received blood transfusions to maintain hemoglobin concentrations at minimally effective levels. Thus many dialysis patients were exposed to substantial amounts of HLA antigens and became sensitized because of the transfusions. There have been several strategies of treating blood to remove the nucleated cells that carry these antigens prior to transfusion. However, it appears that even blood treated by the most modern techniques is not free of the sensitizing elements.

Over the years, there have been several methods of determining whether patients who have been exposed to foreign human antigens have developed antibodies to them and thus have become sensitized. Until recently, the most widely accepted method is known as panel reactive antibody (PRA), which is a measure of the percentage of human antibodies in a transplant candidate's blood. The traditional method of measuring these antibodies was to place serum of the patient in each of 40 test wells that contained cells from a broad base of potential donors. The number of wells in which there was clear interaction of the candidate's serum with blood of potential donors was used as the basis of determining the percent of the general population against which the donor had antibodies. For example, if there was reaction to 20 of the 40 test wells, the candidate was said to have 50% sensitization. By identifying the HLA antigens in each of the wells, one could even predict whether a candidate would have antibodies against a specific potential donor. These old techniques recently have been replaced by more modern tests of antibodies that identify specific HLA antigens to which the candidate has developed. Combining information about specific HLA antibodies and the information about the relative incidence of these antibodies in a donor population provides a newer method of describing a candidate's transplant potential. Furthermore, this new technique can pre-identify donors with whom the candidate should not even be matched.

There are at least two ways in which the development of anti-HLA antibodies in a transplant candidate may affect the outcome of a subsequent kidney transplant. In the first case, a patient who has been sensitized to HLA antigens prior to transplant will have antibodies directed against those antigens and, in general, will not be able to receive an organ transplant from a potential donor who has one or more of those HLA antigens. Obviously, a more highly sensitized transplant candidate will require a larger group of potential donors in order to find one to whom he is not sensitized. If the transplant candidate is sensitized against all potential living donors, the candidate's only option is to receive a deceased donor transplant. In general, deceased donor transplants have higher percentages of acute rejection episodes a shorter half-life than those received from living donors. Moreover, since the pool of potential satisfactory deceased donors is smaller for a sensitized candidate than a non-sensitized candidate, the sensitized candidate must wait longer until an appropriate deceased donor is identified. Indeed, in some cases, a very highly sensitized candidate never finds an appropriate organ donor. Analysis from the SRTR has also shown that transplant candidates who wait long periods of time before receiving a kidney transplant have worse outcomes than those who wait only a short time. In addition, analyses from the SRTR also have demonstrated a correlation between the development of sensitization prior to transplant and transplant outcomes: sensitized patients have less successful kidney transplants than unsensitized recipients. Overall, therefore, the development of sensitization against HLA antigens prior to transplantation has been correlated with greater length of time prior to transplantation, difficulty in identifying potential donors and with decreased success of the kidney transplant.

Several decades ago, an interesting correlation between exposure to blood transfusions prior to transplant and improved transplant outcomes was noted. This "transfusion effect" was first noted for deceased donor transplant recipients. Based on that observation, a deliberate strategy of providing blood from the potential living donor to the recipient candidate prior to transplantation was developed and was known as "donor specific transfusions". It should be

noted that provision of donor specific transfusions led to a 15–30% sensitization in the recipient candidates who therefore could not receive the transplants from those potential donors. The transplant candidates who received donor specific transfusions and were not sensitized and who subsequently received kidney transplants from those donors had better one and three-year graft survival rates than un-transfused kidney transplant recipients. Whether the improvement in graft survival in the transplanted recipients was due to pre-selection of inappropriate donors (i.e. the development of antibodies to donors whose kidneys would have been rejected anyhow) or whether it was due to an active tolerance-inducing mechanism of the blood transfusions themselves was never established. Although donor specific transfusion protocols were successful, improvement in graft survival through the implementation of modern immunosuppressants overtook those beneficial effect and those transfusion protocols have not been utilized for the past two decades. There have been some promising preclinical studies of the use of donor specific bone marrow transfusions in experimental transplantation but those have not yet been extended to common human procedures. Overall, the issue of pre-exposure of transplant candidates to foreign donor antigens currently seems to be detrimental rather than beneficial. Prevention of exposure to HLA antigens prior to transplantation seems to be an appropriate strategy.

Finally, modern immunosuppressive protocols sometimes can result in bone marrow suppression at least during the first few months following transplantation when the doses of the medications or antibodies are at their highest levels. Indeed, many of these recipients may require ESAs or blood transfusions to maintain appropriate hemoglobin levels while receiving the early course of immunosuppression. Appropriate levels of hemoglobin to be maintained in this setting have not been established but most programs prefer to avoid transfusions after transplantation in order to avoid exposure to foreign antigens as well as potential infectious agents.

Overall, therefore, it appears as if the balance of data suggests that it is most appropriate to avoid sensitization prior to or subsequent to kidney transplantation. Currently the most successful method of avoiding sensitization is to avoid exposure to foreign human antigens.

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On Behalf of ASN