A GPS for finding the route to transplantation for the sensitized patient

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Purpose of review
To identify factors that affect the choice of route to renal transplantation for the sensitized patient. The evolution of protocols for transplanting sensitized patients has been desensitization (DES), paired donation, and most recently, paired donation combined with DES. Use of these protocols has revealed various factors that influence which route is the most likely to work for a given patient.

Recent findings
The data indicate that patient blood type and HLA sensitization have the dominant influence on what route is best for a patient but numerous other factors, particularly the number, HLA type, and ABO type of donors a patient brings to a program will also affect the likelihood of transplantation. The distribution of these factors among patients transplanted or unable to find a compatible donor can be used to calculate the probability of transplantation via paired donation.

Summary
Kidney paired donation with or without DES provides benefits that cannot be achieved with DES alone. However, DES may provide the fastest route to transplantation.

Keywords
desensitization, HLA antibodies, kidney paired donation, transplantation

INTRODUCTION

Patients who, because of sensitization, previously could not be transplanted or were transplanted only after prolonged waiting times are now being transplanted successfully through four protocols: desensitization (DES), kidney paired donation (KPD), KPD combined with DES (KPD-DES), and acceptable mismatch. DES provides an opportunity to transplant patients with donors to whom the patient is sensitized by eliminating donor HLA-specific antibody (DSA) or reducing it to a level deemed well tolerated for transplantation [1]. The two protocols in widest use are monthly treatment with high-dose intravenous pooled human immunoglobulin (IVIg) and rituximab [2] and plasmapheresis combined with low-dose IVIg [3,4]. Overall, DES reduces waiting time for patients that, in turn, decreases dialysis-associated morbidity [5] and mortality [6,7▪▪]. For others, particularly those with very broad sensitization, DES provides what may be the only possible means of transplantation. However, DES is accompanied by an increased risk of antibody-mediated rejection (AMR) and some degree of health risk [8,9]. KPD seeks to circumvent immunologic barriers by exchanging original, incompatible donors between patients with donors who are compatible [10,11]. Additionally, KPD may reduce the degree of HLA mismatch, which is strongly associated with both de-novo and expanded sensitization [12–14], it may avoid repeating an HLA antigen mismatch present in a previous donor, and may result in donor–recipient pairs that are better matched for age. These benefits would likely be expanded by including compatible pairs in a KPD program [15,16▪]. KPD-DES matches patients with donors to whom they have DSA that is weaker than the antibody to the original donor and that can be eliminated or substantially reduced via DES [10,17]. KPD-DES may

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KEY POINTS

- In addition to eliminating or removing immunologic barriers to transplantation, KPD and KPD-DES provide benefits that cannot be achieved with DES alone including better HLA and age matching.
- Desensitization may provide the fastest route to transplantation.
- Data from a center's program can be used to calculate the probability of achieving transplantation via KPD or KPD-DES.
- The number of original donors and their HLA and ABO types can affect the opportunity for a patient to be transplanted via KPD or KPD-DES.

also provide the additional benefits such as better HLA or age match. The fourth protocol, matching patients with deceased donors who have 'acceptable mismatches' – that is, those to whom the patient is not sensitized – is used predominantly in Eurotransplant that requires sharing for such matches [18]. This review will focus on DES, KPD, and KPD-DES protocols.

Montgomery [19] has described an algorithm for determining which protocol may best fit a patient on the basis of sensitization: DES is well suited to broadly sensitized patients who are difficult to match but whose DSA is of sufficiently low titer to achieve successful DES; KPD is most successful for patients with a relatively narrow breadth of sensitization but who have high-titered DSA to their original donor; KPD-DES provides an opportunity to transplant broadly sensitized patients whose DSA to their original donor is strong but who have other weaker antibodies that can be readily overcome via DES. For some patients, no one of these protocols will be an obvious choice. This review will discuss other factors that may further identify the best route to transplantation.

PROGRAM-SPECIFIC FACTORS

When transplanting sensitized patients, there is an absolute need for an efficient, high-quality antibody monitoring program that includes both crossmatch testing and antibody screening and characterization [20▪,21]. Multiplex bead assays lend themselves readily to rapid and accurate monitoring for DES. These tests provide a rapid turn-around time and a high degree of sensitivity and specificity. However, the high sensitivity of these assays increases their susceptibility to interference by substances in patients' serum such as therapeutic agents and non-HLA antibodies [22–24] and to day-to-day and lot-to-lot variability. Optimizing the use of these assays requires reducing interference to the extent possible and expertise in analyzing results [20▪]. Monitoring both prior to and after transplantation is essential. Prior to transplantation and during DES treatment, monitoring measures the success of the treatment. The increased rate of AMR that occurs in desensitized patients indicates that they are at risk for a rebound of DSA. Therefore, close monitoring, particularly during the first 2 weeks after transplantation, is essential but should also be continued, albeit less frequently, for the life of the graft. The program should also have defined levels of DSA known to be amenable to treatment and treatment goals that may vary from complete elimination of DSA to reduction of DSA to a level determined safe for transplantation. Gloor *et al.* [25] have correlated the risk of AMR with pretreatment levels of DSA. Reinsmoen *et al.* [26] have correlated the level of antibody observed after treatment is initiated with the risk of AMR, thus, indicating that a DSA threshold deemed acceptable for transplantation [21]. The variability among different assays and among laboratories combined with differences in treatment protocols dictate that each center should determine the antibody level permissible for transplantation. Even if a compatible donor is identified through KPD, sensitized patients are at an increased risk of developing DSA following proinflammatory events such as trauma and infection or transfusion [27,28] and should be monitored closely both before and after transplantation. Further, antibodies may be transient so that determining sensitization accurately is dependent on the serum specimens available. Although it has long been held that antibodies present only historically did not reduce graft function or graft survival, more recent data suggest that DSA present historically when of sufficient strength to yield a positive cytotoxicity crossmatch represents an increased risk for AMR [29]. We have demonstrated that quantification of HLA-specific B cells by staining B cells with HLA tetramers, permits identification of sensitization among patients without antibody to the tetramer HLA and predicts patients who will have a reappearance of that antibody following transplantation [30]. In a KPD-DES program, determination of antibody specificity and strength provides an opportunity to perform virtual crossmatches with potential donors to reduce the amount of crossmatch testing needed that, in turn, reduces the frequency of phlebotomy that potential donors must undergo and eliminates

unnecessary shipment of blood specimens in regional and national programs [31▪,32,33].

It has become evident that antigens encoded by any HLA locus, HLA-A, HLA-B, HLA-Cw, HLA-DRB1, HLA-DRB3-5, HLA-DQA, HLA-DQB, HLA-DPB, and HLA-DPA, can be a target of an antibody-mediated response [33–35]. Commercial kits are available for identifying the antigens at all HLA loci and differentiating among allele groups or alleles in many cases. Therefore, it is incumbent upon and feasible for laboratories to determine complete phenotypes that include all of these HLA loci. Patients with a very rare HLA allele may make antibody that appears to be specific for their own antigen but is, in fact, specific for a different allele within the same antigen group. A rare allele in a donor may be mistaken for an incompatible antigen, although it may not be. Such cases of apparent auto-HLA antibody or cases in which a negative crossmatch occurs when a positive crossmatch is predicted should have the allele of the antigen in question identified through high-resolution typing procedures.

Mutliple criteria, including HLA antibody specificity, ABO blood group, previous mismatches, HLA match, and age, can be applied to matching donors and recipients in KPD. Considering the complexity generated by using multiple criteria, identifying potential matches is best done by a computerized matching program that is both faster and more accurate than manual evaluation of matches. Further, computerized match programs facilitate the identification of matches involving multiple donor–recipient pairs that may be the only opportunity for finding a matched donor for some recipients [36]. It is also possible to use HLA allele and haplotype frequencies to determine the probability of finding a particular degree of HLA and ABO match for a sensitized patient.

All KPD and KPD-DES programs involve numerous personnel for medical evaluation of donors and recipients, identification of potential matches, coordinating the logistics of timing, testing, and transportation of specimens and donors or donor organs [1,37]. Completing all medical evaluations and laboratory testing, particularly in complex cases involving multiple donor–recipient pairs and two or more transplant centers, may take a substantial amount of time, during which one or more parties may become temporarily unavailable. Successful transplantation of KPD cases requires dedicated personnel and timely communication among medical and laboratory personnel, patients, and donors.

PATIENT-SPECIFIC FACTORS

The most critical patient-related factors are the strength and breadth of HLA sensitization and ABO blood type. These factors are known to correlate with the probability of being transplanted and for those who are transplanted, with waiting time. An accurate measure of the breadth of sensitization is given by the percentage of unrelated donors who have an antigen considered unacceptable for transplantation. In the USA, this is referred to as the calculated panel-reactive antibody (CPRA), although there are additional terms used in other countries [38,39▪▪]. CPRA is an accurate measure of HLA antibody breadth but it does not tell the entire story, particularly in patients with high CPRA values (>80%). For example, a patient with high CPRA and strong DSA to an intended donor may have antibodies of lower strength to other antigens making KPD-DES a reasonable choice. Additionally, comparable high CPRA values may not reflect the true likelihood of finding a compatible donor. We simulated two patients with CPRA equal to 98%. One patient had antibodies only to HLA-A antigens, whereas the second patient had antibodies to both HLA-A and HLA-B antigens. The frequency of compatible donors for the first patient was 0.02, whereas for the patient with antibodies to both HLA-A and HLA-B, the frequency was 0.016. The difference would be irrelevant to a local or regional registry with 100 or so donors. However, with a registry of 1000 donors, as might exist in some regional or national registries, the difference in the probability of finding a suitable donor is significant ($P = 0.02$).

HLA antibody strength impacts DES protocols as it correlates with the number of treatments needed [41]. However, in addition to strength, antibody specificity affects the outcome of DES with the plasmapheresis low-dose IVIg protocol in which DSA elimination is observed for 75% of class I-specific antibodies, approximately 50% of antibodies to DRB1 and DQB antigens, but only 10% of antibodies to DR51, DR52, or DR53 antigens [42].

ABO type of the patient is a significant factor for transplanting via the KPD route because KPD pools have a skewing toward donors with blood type A and recipients with blood type O [15,16▪]. This further reduces the match rate, particularly for O recipients. Some programs, such as ours, are willing to cross the blood group barrier in order to reduce the HLA DSA strength in very broadly sensitized patients but isohemagglutinin strength must be not be too high. Waiting time may be a factor for medical, psychological, or logistical reasons.

Table 1 shows the distribution of CPRA values, results of crossmatch with original donors, mean crossmatch titers, ABO distribution, and waiting times among four groups of sensitized patients evaluated and/or transplanted at the Johns Hopkins Comprehensive Transplant Center between 2006

Table 1. Patient-related factors: data on sensitized patients in the Johns Hopkins Incompatible Transplant Program

	DES	KPD	KPD-DES	Not transplanted
Number	101	35	55	39
CPRA means	46.0 ± 36.9	30.9 ± 36.5	65.0 ± 32.3	86.9 ± 11.9
CPRA medians	54	9	98	94
XM[a]				
CDC[b]	25	14	44	36
FCXM[c]	55	10	7	2
DSA[d]	23	11	4	1
GM-CDC[e]	6.5	45.2	17.9	55.9
Percentage ABO O	48.5	37.1	34.5	43.6
Waiting time[f] means	386 ± 321	520 ± 366	611 ± 414	931 ± 534
Waiting time[f] medians	276	412	546	851

CPRA, calculated panel-reactive antibody; DES, desensitization; DSA, donor-specific antibody; KPD-DES, kidney paired donation combined with desensitization.
[a]Number of patients with various crossmatch results with original donor.
[b]CDC, Complement-dependent cytotoxicity crossmatch.
[c]FCXM, Flow cytometric crossmatch.
[d]Crossmatch negative, donor HLA-specific antibody present.
[e]GM, Geometric mean of CDC crossmatches with original donors.
[f]Waiting time in days.

and 2011. These patients included those who were transplanted via DES, transplanted by KPD (with or without DES), and patients for whom a donor has not been identified, to date. The ratio of mean-to-median values within each group show that mean CPRA values are skewed for both KPD and KPD-DES groups. The mean CPRA of the KPD group was skewed toward higher values by high CPRA outliers and the mean of KPD-DES was skewed toward lower values. Waiting times for all groups were skewed by high-value outliers, inflating the mean waiting times.

DONOR-SPECIFIC FACTORS

Donor HLA and ABO type affect the likelihood a donor will be matched with a recipient in a KPD program. Broadly sensitized patients frequently have a limited array of antibodies that are specific for epitopes shared by multiple antigens [42,43]. The effect is that highly sensitized patients have similar antibody profiles that put them in competition for donors with similar HLA types that are often comprised of less common antigens [17]. Donors who are homozygous at one or more HLA loci have fewer possible mismatches. Such donors are more likely to match with broadly sensitized patients and may increase the chance of avoiding a repeated mismatch. Donors who are blood type O can donate to patients of any blood type. Thus, donors who are homozygous at one or more HLA loci and/or are blood type O are more readily matched with patients in a KPD registry and, by default, increase the transplant opportunities for their original recipients if they have favorable HLA and ABO phenotypes. The number of donors brought forward by an individual patient may also increase the opportunity for transplantation for that patient in either the DES or KPD programs. Table 2 shows the donor factors for the KPD, KPD-DES, and patients not yet transplanted shown in Table 1. The improvement in compatibility achieved with paired donation is notable by the reduction in both the number of positive crossmatches and the mean crossmatch titers by the reduction in mismatched antigens indicated by the increase in homozygosity among exchange donors. It is also notable that KPD without the need for DES was facilitated by the availability of exchange donors with some degree of homozygosity that, in 14 of 19 cases, involved at least one HLA antigen that was matched with the recipient.

DETERMINING THE MOST LIKELY ROUTE TO TRANSPLANTATION

Because, as noted above, KPD has advantages not available with DES alone, we will begin with the premise that this should be the first consideration. Then, several factors can be used in a Bayes' calculation to determine the probability of achieving transplantation via KPD or KPD-DES. The generic calculation is given below and an example using data from the Johns Hopkins program (Table 3) is provided.

Table 2. Donor-related factors: data on donors in the Johns Hopkins Kidney Paired Donation Program

	KPD		KPD-DES		Not transplanted
Donor	Original	Exchange	Original	Exchange	Original
CDC[a]	14	0	44	2	36
FCXM[b]	10	0	7	35	2
DSA[c]	11	0	4	18	1
No DSA	0	35	0	0	0
GM-CDC[d]	45.2	0	52.8	2	55.9
Homozygosity[e]	31.4	57.1	45.5	49.1	28.2
Original donor blood type 0 (percentage)	45.7		49.1		30.7
Number of donors evaluated	4.7 ± 3.1		5.4 ± 4.3		3.7 ± 2.7

Donor factors are shown for original donors for all patients in KPD program and for exchange donors for transplanted patients. DSA, donor-specific antibody; KPD-DES, kidney paired donation combined with desensitization.
[a]Number with positive cytotoxicity crossmatches.
[b]Number with positive flow cytometric crossmatches.
[c]Number with negative crossmatch but DSA present.
[d]Geometric mean of CDC crossmatch titers.
[e]Percent of original donor with one or more HLA homozygosity.

P (KPD): prior probability of KPD – based on frequency of KPD transplants among patients entered into KPD program

P (KPD-DES): prior probability of KPD-DES – based on frequency of KPD-DES transplants among patients entered into KPD program

P (No Tx): prior probability of no transplant – based on frequency of patients not transplanted among patients entered into KPD program

1A: frequency of KPD patients with CPRA less than 80%

1B: frequency of KPD patients with original donor blood type O

1C: frequency of blood type O KPD patients

1D: frequency of KPD patients who had more than three potential donors

These values are then given for KPD-DES patients using the prefix 2 and for patients not transplanted using the prefix 3.

The equation for the probability of KPD given the data is:

$$P(\text{KPD}|\text{data}) = \frac{P(\text{KPD})(1A)(1B)(1C)(1D)}{P(\text{PDK})(1A)(1B)(1C)(1D) + P(\text{KPD-DES})(2A)(2B)(2C)(2D) + P(\text{NoTx})(3A)(3B)(3C)(3D)}$$

Example

Patient has a CPRA of 50, original donor is blood type O, the patient is blood type O, original donor is homozygous at the HLA-A locus, and the patient has brought four potential donors.

$$P(\text{KPD}|\text{data}) = \frac{(0.27)(0.83)(0.46)(0.37)(0.31)(0.51)}{(0.27)(0.83)(0.46)(0.37)(0.31)(0.51) + (0.43)(0.51)(0.49)(0.53)(0.46)(0.62) + (0.30)(0.28)(0.31)(0.77)(0.28)(0.23)} = 25.6\%$$

Table 3. Johns Hopkins data used in Bayes' equation

	KPD	KPD-DES	Not transplanted
Prior probability	0.27	0.43	0.30
CPRA less than 80%	0.83	0.51	0.28
Original donor ABO is O	0.46	0.49	0.31
Patient ABO is O	0.37	0.53	0.77
HLA homozygosity in original donor	0.314	0.455	0.282
More than three original donors available	0.51	0.62	0.23

Values in the table are the distributions of the various factors among patients transplanted via KPD, KPD-DES, or not yet transplanted. The prior probability is the portion of patients in each of those categories. HLA homozygosity refers to the occurrence of a homozygous antigen at one or more loci in the original donor. CPRA, calculated panel-reactive antibody; KPD-DES, kidney paired donation combined with desensitization.

Using the same equation, the probabilities of transplantation by KPD-DES and of no transplant are 68.9 and 5.5%, respectively. Thus, for a program with the capabilities of both KPD and KPD-DES, the probability the patient will be transplanted via one of these options is nearly 95%. Each program must determine the threshold of probability that is reasonable to have a goal of KPD and/or KPD-DES for a given patient. As noted above, there may be factors, such as the need for the shortest time to transplant, that may affect the choice of protocol. Also, although KPD and KPD-DES do offer important advantages compared with DES, over time, patients for whom an acceptable match/mismatch cannot be found will accumulate in a KPD registry. For these patients, DES with their original donor may be the preferred route to transplantation.

CONCLUSION

DES, KPD, and KPD-DES have been used to transplant sensitized patients successfully. Maintaining any of these protocols requires program resources beyond that usually needed for a transplant program. Although a patient's sensitization and blood type are the dominant factors in determining which of these three modalities may best suit a particular patient, numerous other factors such as timing of the transplant, the number of donors associated with the patient, and the HLA and ABO type of those donors can also have an effect. KPD with or without DES provides benefits that cannot be achieved with DES alone. However, because patients most readily matched will be transplanted more quickly, patients with multiple, strong antibodies will accumulate in a KPD program, over time increasing competition for the few donors who are compatible with such patients. Thus, some patients are unlikely to find a suitable donor or be readily desensitized.

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Conflicts of interest

The authors have no conflict of interest relevant to this article.

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