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The 3P’s of transplant modelling to inform clinical decision-making: predictability, probability and possibility

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Transplantation of highly-sensitized (HS) patients remains a considerable challenge for transplant programs worldwide. Approximately 5-9% of all potential transplant candidates in the United States and Europe are highly-sensitized\(^1\). The annual transplantation rate for these patients is reduced by at least 2-fold compared to the non-sensitised individuals\(^2\).

Consequently, these patients may wait twice as long on the transplant waiting list as the unsensitized patients and are more likely to be delisted or die on the waiting list. Even with the availability of potential living donors, transplantation is not always possible among HS patients. Desensitisation of a living donor/recipient pair to overcome low level incompatibility and the deleterious donor-specific anti-HLA antibodies is a reasonable option. However, outcomes after desensitization are less optimal and these patients are more likely to experience premature allograft failure or treatment-related complications\(^3\).

The paired kidney exchange program has been successful to match donor-recipient pairs, often without the necessity to overcome the HLA barrier through desensitization\(^4\). Through this strategy, an improvement in the transplantation rate of HS patients has been successfully attained. In this study, de Klerk M and colleagues designed a computer program, the Computerised Integration of Alternative Transplantation (CIAT), which integrated all alternative living donor kidney transplantation programs in the Netherlands. The model aimed to optimize the number of transplant matches for HS patients and maximize the total number of transplants for the population of interests\(^5\). The CIAT software utilises a mathematical algorithm that effectively deals with the multiple criteria being imposed on the allocation of donors to potential transplant candidates in a paired kidney exchange system. This algorithm has been validated using kidney-exchange data from the Netherlands and United States and appears to be effective, even for large, but realistic patient-donor pools\(^6\).
Using data from all recipients registered on the Eurotransplant waiting list and potential live-donors (including unspecified kidney donors) from Rotterdam between 2015 and 2016, the authors reported an additional seven (out of 20 (35%)) selected highly-immunized (sHI) patients may be matched for transplantation using the CIAT simulation (i.e. 1 sHI patient transplanted in reality vs. 8 sHI patients matched in the CIAT simulation modelling).

However, this improvement in transplant potential was probably not unexpected because an increase in the number of donor/patient pairs and unspecified donors available for matching would inevitably increase the probability of a potential match for a particular patient. In addition, the authors also accepted high-risk ABO-incompatible (titres below 1:512) and positive complement-dependent cytotoxicity cross-match (CDC-XM) transplants in potential candidates with no compatible matches after a pre-specified period of wait-time and failed match runs. Of the eight sHI patients matched using the CIAT simulation model, six (75%) had moderate or high mean fluorescent intensity (MFI) donor-specific anti-HLA antibody (DSA; 3 patients had DSA above 8000MFI), and two patients had positive CDC-XM to the CIAT matched donor. Four (50%) patients had positive T or B cell flow-XM, with 3-times the channel shift thresholds for a positive test result.

However, there are important caveats, and these must be recognized when interpreting the study findings. The three key assumptions included in the modelling were: 1) matched donor/patient pairs who were CDC or flow-XM positive or had high ABO titres received successful desensitization prior to proceeding to transplantation; 2) the model was unable to account for patients (sHI and non-sHI patients) who had been transplanted earlier through the standard allocation algorithm. These patients were not available for the simulation, and the downstream effects on subsequent donor kidney allocation/acceptance were not observed; and 3) clinicians must be willing to accept a chain that may require desensitization for the donor/recipient pairs with HLA incompatibility, and a program that prioritized sHI patients.
Such program could inadvertently reduce the probability of successful match(es) for other patients.

Nonetheless, findings from this study support a multi-faceted approach that integrates a gamut of novel strategies to improve the transplant potential of HS, difficult-to-match patients. Information provided by this simulated model is also useful to inform clinical decision-making process and the trade-offs when choosing the alternatives, ensuring that the desired impact of the modification in matching policy is achieved. However, one must be cautioned regarding the clinical applicability of this modelling, as these findings are results of the matches, and not the actual transplantations. Ultimately, the short and long-term outcomes of these potential transplants are unknown.
References


