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The Impact of Withdrawal of Maintenance Immunosuppression and Graft Nephrectomy on HLA Sensitization and Calculated Chance of Future Transplant

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Background. The development of HLA antibodies towards a failing renal allograft is a barrier to retransplantation. This study aimed to compare the formation of HLA donor-specific antibodies (DSA) in patients undergoing graft nephrectomy and in those with a failed graft left in situ who had maintenance immunosuppression (IS) stopped, and assess the relative impact of IS cessation and graft nephrectomy on future relative chance of transplant (R-CoT). **Methods.** A single-center retrospective study of patients with failed grafts between 2005 and 2015 was performed. Samples were tested for DSA pre-IS wean, post-IS wean, and post-IS cessation. Nephrectomy patients additionally had samples tested for DSA before and after nephrectomy. Calculated reaction frequency (cRF) was determined at each timepoint and entered into the UK Organ Donation and Transplant R-CoT calculator. **Results.** Forty-one patients were included in the study: 24 with nephrectomy and 17 with a failed graft in situ. Patient demographics and duration of IS wean were similar between groups. There was a higher rate of blood transfusion (54% vs 24%) in nephrectomy patients. In patients whose graft remained in situ, cRF rose from 13% pre-IS wean to 40% post-IS wean and 62% after IS cessation. This equated to a reduction in mean R-CoT from 54% to 46% at 5 years. In patients undergoing nephrectomy mean cRF rose from 31% pre-IS wean to 69% post-IS wean and 89% post-IS cessation. Mean R-CoT fell from 54% to 42% at 5 years. **Conclusions.** A stepwise increase in cRF with reduced chance of transplant was observed in both groups as IS was withdrawn, with a similar pattern irrespective of graft nephrectomy. Calculated reaction frequency was higher in the nephrectomy group. The risks and benefits of stopping IS need to be carefully considered on an individual basis to maximize chance of future transplant.

(*Transplantation Direct* 2018;4: e409; doi: 10.1097/TXD.0000000000000848. Published online 23 November, 2018.)

Received 13 September 2018. Revision requested 19 June 2018.

Accepted 22 October 2018.

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The authors declare no funding or conflicts of interest.

A.M.S.A.N. participated in performance of research, data analysis, and writing of the article. S.M. participated in performance of research and data analysis. D.M.T. participated in research design, data analysis and writing of the article. L.K.H. participated in research design, data analysis, and writing of the article. R.K.B. participated in research design, performance of research, data analysis, and writing of the article.

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ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000000848

Despite an improvement in long-term renal allograft survival over the last decade, patients with a failed graft constitute 4% of the hemodialysis population and 20% of the cadaveric renal transplant waiting list.[1,2] Their chance of receiving a further transplant is influenced by HLA sensitization, and graft survival may be reduced if transplanted in the presence of preexisting donor-specific antibodies (DSA).[3,4] Risk factors for HLA sensitization in the context of a failing graft include the weaning of maintenance immunosuppression (IS) (planned or noncompliance) and transplant nephrectomy.[3] Currently, however, there is limited data on how chance of future transplant is influenced by these factors.

Graft nephrectomy is performed for a number of indications. These include creation of space for future transplant and to manage chronic rejection manifest by graft pain, hematuria, hypertension, and anemia.[5,6] It is recognized that de novo DSA can form postnephrectomy in up to 80% of patients,[7] but the underlying mechanism is unclear. Endothelial injury at the time of nephrectomy creates a proinflammatory state and may induce DSA formation.[8] Studies have also demonstrated DSA adsorbed onto graft nephrectomy specimens,

suggesting that preexisting DSA may be released into the circulation after graft removal.[9,10] Finally, weaning of IS, which often occurs contemporaneously with nephrectomy due to infective and malignant risks, has been reported as an independent predictor of sensitization after nephrectomy.[11]

There is conflicting evidence to guide the management of IS after graft failure. Patients relisted for transplant maintained on dual-agent IS have a reduced risk of sensitization compared with those on a single agent or no IS.[12] The risk of antibody formation and sensitization, therefore, needs to be balanced against long-term infective, cardiovascular and malignant risks.[13] Current guidelines recommend continuing IS if there is potential for preemptive retransplant or retransplant within 1 year of return to renal replacement therapy (RRT).[14]

Up to 60% of patients are sensitized after graft failure, rendering them more difficult to retransplant with longer waiting times.[15] In the United Kingdom in 2017, 24% of the waiting list had a previous transplant but only 14% of transplants performed were regrafts.[15] Mortality on dialysis is 80% higher in patients relisted after graft failure than in those awaiting their first allograft. This risk is greatest immediately upon returning to dialysis but persists for at least 10 years.[16] It is therefore vital to give these patients the best chance of prompt retransplantation. To ensure this, we need to expand our understanding of the impact of nephrectomy and withdrawal of IS on the formation of HLA antibodies.

In the United Kingdom, the relative chance of transplant (R-CoT) calculator is used to calculate and communicate the impact of sensitization on transplant waiting time for an individual patient. It was generated by the Statistics and Clinical Audit Department within NHS Blood and Transplant (NHSBT), and reports the percentage of patients with similar clinical demographics transplanted with a donation after brainstem death (DBD) deceased donor within a given timeframe.[17]

We sought to understand the relative impact of graft nephrectomy and weaning of maintenance IS on the formation of HLA antibodies in renal transplant patients at our center and the effect this has on future chance of transplant using the R-CoT calculator.

MATERIALS AND METHODS

Ethical Approval

This was a retrospective study analyzing routinely collected clinical data. The study details were assessed through the Health Research Authority which indicated that NHS Research Ethics Committee approval was not required.

Patient Population

Patients with a failed renal transplant returning to RRT between January 2005 and December 2015 were identified through a systematic search of the local database. Patients choosing conservative management after graft failure were excluded from the study. Patients were divided into 2 cohorts according to whether graft nephrectomy was performed (nephrectomy group) or the failed graft remained in situ (graft in situ [GIS] group). Patients without HLA antibody test results or stored samples suitable for analysis were excluded.

Demographic information collected included; age, gender, cause of graft failure and graft nephrectomy indication (where applicable). Exposure to potential confounding sensitizing events close to graft failure was collected, comprising blood transfusions and episodes of antibody mediated rejection (AMR).

Information was recorded on maintenance IS, the timing and method of first reduction to IS and date of IS cessation (withdrawal of all immunosuppressant agents). There was variation in the timing of reduction in IS between individuals. In the majority of cases it correlated to imminent return to dialysis or nephrectomy. In a minority, it was in an attempt to preserve graft function.

HLA Antibody Testing

Samples were tested for HLA antibodies (class I HLA-A, -B, -C and class II HLA-DR, -DQ, -DP) at the following timepoints: before reduction in IS (pre-IS wean), after reduction in IS (post-IS wean), and after IS was stopped (post-IS cessation). In patients undergoing graft nephrectomy, samples were tested prenephrectomy and postnephrectomy.

Samples were screened for HLA antibodies using LABScreen Mixed beads. Positive samples were tested using LABScreen Single Antigen Class I and II beads (One Lambda Inc, Canoga Park, CA) to determine antibody specificity. Donor and recipient HLA typing was performed using LABtype Luminex SSO (One Lambda). Presence of HLA-specific antibodies was used to determine the calculated reaction frequency (cRF). A mean fluorescence intensity (MFI) of over 1000 was generally deemed to be positive.[18] In accordance with recent STAR working group recommendations, an MFI below 1000 could be considered false negative when the antigen belonged to a cross-reactive group or shared epitopes with other reactive alleles. An MFI above 1000 was considered false positive if reactivity was against a denatured epitope, in a nonspecific pattern or directed against an autoantigen.[18]

Chance of Transplant

The R-CoT calculator is computer software that provides meaningful information on anticipated waiting time, tailored to an individual's details. This statistical model considers patient variables against historic UK data and reports the percentage of patients with similar clinical demographics who received a DBD kidney within a given timeframe.

The variables used in generating the R-CoT are as follows: blood group, matchability, age at registration, transplant center, sensitization (standardized cRF), previous graft failure within 180 days, ethnicity, periods of suspension, homozygosity at HLA-DR and HLA-B, and number of previous transplants.[17] Matchability is classified as easy, moderate, or difficult. This is based on the number of blood group identical, well (000 for HLA-A, -B, -DR), or favorably (100, 010, or 110) HLA-matched donors that the recipient would be matched with from a standardized pool of 10 000 recent UK deceased donors.

To determine the impact of IS and nephrectomy on R-CoT, the mean cRF at each timepoint was inputted into the calculator. Because we wished to only determine the effects of IS wean and graft nephrectomy on R-CoT, all other variables were set to represent average patient characteristics at our center. This comprised the following: registration age of 40 to 49 years, blood group O, white, no previously failed graft within 180 days, not suspended for 25% or greater of the time, heterozygous at HLA-B and HLA-DR, and relisting after single graft failure.

Statistical Analysis

Continuous variables are expressed as medians and interquartile ranges (IQRs) and were analyzed using the Mann-Whitney *U* test. Nominal variables were analyzed using the Fisher exact test. Changes in cRF and R-CoT were analyzed using a 2-way analysis of variance. Changes in HLA antibody positivity and number of highly sensitized individuals were analyzed using the Fisher exact test. A *P* value less than 0.05 was deemed statistically significant.

RESULTS

In total, 74 patients had a failed renal allograft between 2005 and 2015, and 71 returned to RRT. Graft nephrectomy was performed in 29 patients. Samples for HLA antibody testing were available in 41 (58%) patients: 24 (58%) from the nephrectomy group and 17 (42%) from the GIS group.

Patient Demographics

Patient demographics were similar between groups (Table 1). There was a male preponderance, comprising 58% of patients (14/24) in the nephrectomy group and 71% (12/17) in the GIS group ($P = 0.36$). Within the nephrectomy group, there were 16 cadaveric transplants, 2 simultaneous kidney pancreas transplants and 6 live donor transplants. In the patients with simultaneous kidney pancreas transplants, the pancreas had also ceased to function and was removed. Within the GIS group, there were 11 cadaveric transplants and 6 live donor transplants. The rate of delayed graft function was 29% (7/24) in the nephrectomy group and 18% (3/17) in the GIS group ($P = 0.48$). Median age at graft failure was 47 years in the nephrectomy group (IQR, 38-51) and 51 years in the GIS group (IQR, 27-60) ($P = 0.37$). Relisting for transplant occurred in 92% (22/24) of the nephrectomy group and 94% (16/17) of the GIS group ($P = 1.0$).

The patients were not high immunological risk: there were no highly sensitized individuals' pretransplantation, transplants were ABO- and HLA-compatible, and all patients received standard induction IS. Standard IS changed in 2009 from methylprednisolone induction with maintenance tacrolimus, azathioprine, and prednisolone to methylprednisolone and basiliximab induction with maintenance tacrolimus, mycophenolate mofetil, and prednisolone.

Cause of Graft Failure and Nephrectomy

Graft failure in the nephrectomy group was attributed to rejection in 79% (19/24) of the patients. Other causes included interstitial fibrosis and tubular atrophy with no specific features of rejection (2 patients), primary nonfunction not related to rejection (2 patients), and primary disease recurrence (1 patient). Histological information from explants showed AMR in 25% (6/24), T cell–mediated rejection in 25% (6/24) and mixed rejection in 29% (7/24).

In the GIS group, 10 patients had a biopsy within a year of graft failure. In those undergoing biopsy, histological findings were nonspecific in 4 patients with interstitial fibrosis, tubular atrophy, and microvascular changes. Although this does not exclude an immune-mediated cause, there were no other features of chronic rejection in these biopsies. Recurrence of primary disease was identified in 3 patients and chronic AMR in 3 patients.

Indications for nephrectomy were acute vascular occlusion (1 patient), primary nonfunction relating to nonimmunological events (2 patients), acute rejection refractory to treatment (6 patients), graft tenderness (11 patients), resistant anemia (2 patients), and preparation for retransplant (2 patients).

IS Management

The median time from the start of IS wean to cessation was 424 days (IQR, 134-797) in the nephrectomy group and 428 days (IQR 234-541) in the GIS group ($P = 0.94$). There was a significant difference in time from transplant to graft failure between groups, with a median time of 58 months in the nephrectomy group (IQR, 8-108) and 141 months in the GIS group (IQR, 70-249) ($P = 0.01$). The median time from transplant failure to nephrectomy was 384 days (IQR, 95-453).

In the nephrectomy group, 50% (12/24) of the patients were on triple-agent IS and 50% (12/24) were on dual-agent IS at time of graft failure. Triple-agent IS comprised calcineurin inhibitor (CNI), antimetabolite, and steroid. Dual-agent IS comprised CNI and steroid in 6 patients, antimetabolite, and steroid in 5 patients, and sirolimus and steroid in 1 patient. In the GIS group 29% (5/17) were on triple-agent IS, 65% (11/17) on dual therapy, and 6% (1/17) on single-agent IS. Dual-agent IS comprised CNI and steroid in 8 patients, CNI and antimetabolite in 2 patients, and antimetabolite and steroid in 1 patient. The patient on single-agent IS was on sirolimus.

The pattern of IS wean was similar. In those on triple therapy, cessation of antimetabolite was the most common initial change. In those on dual agents, the initial change was cessation of CNI or antimetabolite.

TABLE 1.

Patient demographics in graft nephrectomy and GIS groups

	Graft nephrectomy (n = 24)	Failed GIS (n = 17)	*P*
Sex, % (n) male	58% (14)	71% (12)	0.36
Age: median (IQR), y	47 (38-51)	51 (27-60)	0.37
Donor type (n)			0.87
• Live donor	6	5	
• DBD	17	11	
• DCD	1	1	
Delayed graft function, % (n)	29% (7)	18% (3)	0.48
Transplant to graft failure, median (IQR), mo	58 (8-108)	141 (70-249)	0.01
Graft failure to nephrectomy, median (IQR), d	384 (95-453)	N/A	N/A
Relisted for transplant, % (n)	92% (22)	94% (16)	1.0

In the nephrectomy group, the median time from first IS wean to nephrectomy was 381 days (IQR, 108-675). All patients were on IS at the time of nephrectomy.

Sensitizing Events

Blood transfusions were administered over the period of IS withdrawal in 54% (13/24) of patients in the nephrectomy group and 24% (4/17) of patients in the GIS group (P = 0.054). Biopsy-proven AMR was reported in 54% (13/24) of patients in the nephrectomy group and 18% (3/17) of patients in the GIS group (P = 0.27). Histological analysis of grafts was available in all nephrectomy patients and 59% (10/17) of GIS patients, which may impact on documented rates of AMR.

Patients with biopsy-proven AMR were more highly sensitized. In the nephrectomy group, mean cRF before IS wean was 43% in those with AMR compared with 25% in those without. In the GIS group, mean cRF before IS wean was 47% in those with AMR compared with 2% in those without.

Impact of IS Cessation on Sensitization and Chance of Transplant

To determine the impact of IS withdrawal on sensitization, samples were tested for DSA pre-IS wean, post-IS wean and post-IS cessation. The time between the IS change and blood sampling in the nephrectomy group was a median of 28 days (IQR, 18-90) pre-IS wean, median of 101 days (IQR, 49-236) post-IS wean, and median of 74 days (IQR, 54-171) post-IS cessation. In the GIS group, timings were a median of 316 days (IQR 106-429) pre-IS wean, median of 105 days (IQR 97-231) post-IS wean, and median of 171 days (IQR 82-425) post-IS cessation.

Table 2 shows the changes in cRF, number of patients with HLA class I and class II DSAs and the R-CoT at 5 years for the 2 groups. There is a significant stepwise increase in cRF (P < 0.001) (Figure 1) and trend toward a rise in number of patients positive for both HLA class I and II DSA in both groups as IS is withdrawn. This correlates to a reduction in R-CoT at 5 years, falling from 54% to 42% in the nephrectomy group and from 54% to 46% in the GIS group. The number of highly sensitized patients rose from 19% to 81% in the nephrectomy group (P < 0.001) and from 0% to 41% in the GIS group (P = 0.006).

We observed both the development of de novo DSAs in those with no previous antibodies and a rise in preexisting DSA as IS was withdrawn in both groups.

Impact of Graft Nephrectomy on Sensitization and Chance of Transplant

The change in cRF, R-CoT, HLA class I and II DSA-positive and highly sensitized patients were examined in relation to nephrectomy (Table 2). The median time from nephrectomy to sample analysis was 60 days (IQR, 36-99 days). A rise in cRF from 58% to 69% was seen after nephrectomy. This corresponds to a rise in the number of patients with both HLA class I and class II DSA. The rise in cRF did not equate to a change in R-CoT at 5 years, which remained at 46%. The number of highly sensitized patients rose from 42% to 54%.

DISCUSSION

The management of patients with a failed renal allograft before retransplantation is a challenging area without a strong evidence base.[14] We have demonstrated that in both patients undergoing nephrectomy and in those whose graft is left in situ, there is a significant stepwise increase in cRF as IS is withdrawn. This is associated with a reduction in chance of transplant within 5 years using the NHSBT R-CoT calculator. This has a potentially major impact on patients, where retransplantation offers improved outcomes over remaining on dialysis.[16]

There are center- and physician-dependent variations in IS management after graft failure. One US study found that IS weaning was largely physician-dependent, but the majority of patients had stopped IS 1 year after returning to dialysis.[19] In our center, the median time between graft failure and cessation of IS was 14 months. Caution is required with withdrawal of IS because this can lead to the formation of HLA antibodies toward mismatched class I and II antigens on the graft.[9,10,20-23] In our cohort, patients who did not undergo graft nephrectomy demonstrated a stepwise increase in cRF and a rise in class I and II DSA as IS was withdrawn. The proportion of patients who were highly sensitized rose from 0% to 41% over this time. Importantly, this correlated to a

TABLE 2.

Mean cRF, number of patients with HLA class I and class II DSA, chance of transplant at 5 years, and percentage of highly sensitized patients with nephrectomy and IS weaning

Nephrectomy							
	Pre-IS wean	Post-IS wean	Post-IS cessation	P	Prenephrectomy	Postnephrectomy	P
Mean cRF	31%	69%	89%	<0.001	58%	69%	0.03
HLA class I DSA-positive (n, %)	10 (42%)	14 (58%)	18 (75%)	0.054	14 (58%)	17 (71%)	0.22
HLA class II DSA-positive (n %)	6 (25%)	16 (67%)	17 (71%)	<0.001	12 (50%)	16 (67%)	0.14
R-CoT at 5 y	54%	46%	42%	—	46%	46%	—
Highly sensitized patients	19%	52%	81%	<0.001	42%	54%	0.37
GIS							
Mean cRF	13%	40%	62%	<0.001			
HLA class I DSA–positive (n, %)	3 (21%)	9 (56%)	10 (67%)	0.04			
HLA class II DSA–positive (n, %)	2 (14%)	6 (35%)	9 (60%)	0.04			
R-CoT at 5 y	54%	46%	46%	—			
Highly sensitized patients	0%	6%	41%	0.006			

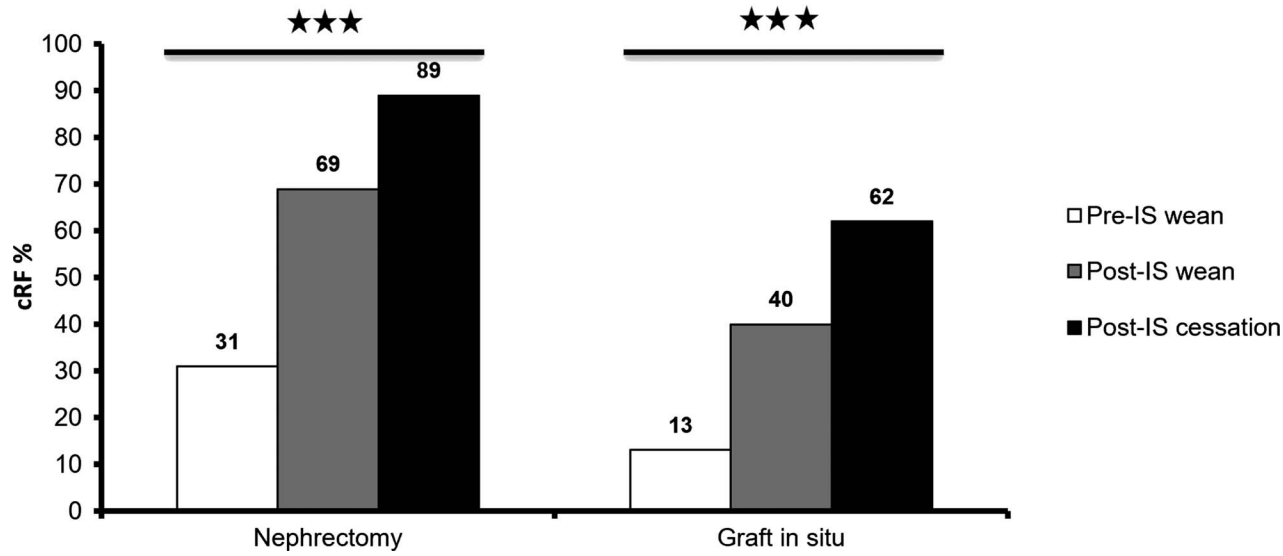

FIGURE 1. Change in cRF as IS is withdrawn in patients undergoing nephrectomy and in those whose graft remains in situ.

reduced R-CoT at 5 years, falling from 54% to 46% as IS was withdrawn.

The impact of graft nephrectomy on sensitization is much debated.[7,9-11] Reduction in IS often occurs contemporaneously with surgery so determining the independent effect of these events is challenging. One theory is that the allograft adsorbs antibodies that are released into the circulation after it is removed.[24] De novo HLA antibodies have been identified within 5 days of nephrectomy, but they can also develop at later timepoints due to donor tissue (usually a vascular patch) left in situ postoperatively.[9,10]

Previous studies have demonstrated that patients undergoing allograft nephrectomy and stopping IS have higher levels of DSAs than those stopping IS without nephrectomy.[7,9] A greater rise in class I DSA has been described postnephrectomy, which could relate to de novo antibody formation against vascular tissue or the release of antibody previously bound to the graft.[25] We found that the percentage of patients with DSA increased after nephrectomy, with class I rising from 58% to 71% and class II rising from 50% to 67%. The mean cRF also increased from 58% to 69%, but this did not equate to a difference in chance of transplant at 5 years. Once IS was stopped, however, the mean cRF rose to 89%, and the percentage of patients with class I and II DSAs were 75% and 71% respectively. Although there may be a differential effect on sensitization dependent on the class of drug withdrawn, we were not able to assess the relative impact of individual immunosuppressant changes on sensitization due to our population size.

At all timepoints, cRF was higher in patients undergoing nephrectomy than in those patients whose graft remained in situ. The nephrectomy group had a significantly earlier graft loss and a higher rate of AMR which may account for this difference.

Because renal transplantation improves patient survival, we need to develop strategies to prevent HLA sensitization after graft failure to facilitate future transplant.[22,26] Current guidelines recommend continuing IS if retransplantation within 1 year is likely.[14] Further work is required to identify which patients are suitable for IS cessation, as well as the optimal timing and protocol for withdrawal of individual drugs.[27]

The rapidity of IS withdrawal may affect the development of DSA, with a prolonged withdrawal (over 3 months) being associated with lower rates of sensitization.[28] Recent work has also suggested that a single dose of IVIg immediately postnephrectomy may prevent the formation of DSA in patients who are not sensitized preoperatively.[29]

Our study has several limitations. This was a single-center retrospective study with small patient numbers. There was a variation in the timing of antibody samples. In particular, post-IS cessation sampling occurred earlier in the nephrectomy group. DSA levels may fluctuate over time, so the differences in sampling between groups could confound results. A prospective study using the same timepoints would be informative. There were also more episodes of AMR and blood transfusions in the nephrectomy group, which may influence the formation of DSA.[30]

Despite these limitations, we demonstrate a clear association with IS reduction and rise in HLA sensitization, and show for the first time how this correlates to a reduced chance of transplant at 5 years using the R-CoT calculator. Understanding this information is important in weighing up the risks and benefits of nephrectomy and IS weaning on an individual basis, and when counseling patients on management decisions and their chance of future transplant.

REFERENCES

1. Collins AJ, Foley RN, Herzog C, et al. US renal data system 2010 annual data report. *Am J Kidney Dis*. 2011;57(1 Suppl 1):A8, e1–e526.
2. Ojo A, Wolfe RA, Agodoa LY, et al. Prognosis after primary renal transplant failure and the beneficial effects of repeat transplantation: multivariate analyses from the United States Renal Data System. *Transplantation*. 1998; 66:1651–1659.
3. Rees L, Kim JJ. HLA sensitisation: can it be prevented? *Pediatr Nephrol*. 2015;30:577–587.
4. Lefaucheur C, Loupy A, Hill GS, et al. Preexisting donor-specific HLA antibodies predict outcome in kidney transplantation. *J Am Soc Nephrol*. 2010;21:1398–1406.
5. Langone AJ, Chuang P. The management of the failed renal allograft: an enigma with potential consequences. *Semin Dial*. 2005;18:185–187.
6. Lopez-Gomez JM, Perez-Flores I, Jofre R, et al. Presence of a failed kidney transplant in patients who are on hemodialysis is associated with chronic inflammatory state and erythropoietin resistance. *J Am Soc Nephrol*. 2004;15:2494–2501.

7. Billen EV, Christiaans MH, Lee J, et al. Donor-directed HLA antibodies before and after transplantectomy detected by the luminex single antigen assay. *Transplantation*. 2009;87:563–569.
8. Locke JE, Zachary AA, Warren DS, et al. Proinflammatory events are associated with significant increases in breadth and strength of HLA-specific antibody. *Am J Transplant*. 2009;9:2136–2139.
9. Del Bello A, Congy N, Sallusto F, et al. Anti-human leukocyte antigen immunization after early allograft nephrectomy. *Transplantation*. 2012;93:936–941.
10. Del Bello A, Congy-Jolivet N, Sallusto F, et al. Donor-specific antibodies after ceasing immunosuppressive therapy, with or without an allograft nephrectomy. *Clin J Am Soc Nephrol*. 2012;7:1310–1319.
11. Augustine JJ, Woodside KJ, Padiyar A, et al. Independent of nephrectomy, weaning immunosuppression leads to late sensitization after kidney transplant failure. *Transplantation*. 2012;94:738–743.
12. Kosmoliaptsis V, Gjorgjimajkoska O, Sharples LD, et al. Impact of donor mismatches at individual HLA-A, –B, –C, –DR, and -DQ loci on the development of HLA-specific antibodies in patients listed for repeat renal transplantation. *Kidney Int*. 2014;86:1039–1048.
13. Pham P, Pham P. Immunosuppressive management of dialysis patients with recently failed transplants. *Semin Dial*. 2011;24:307–313.
14. Andrews PA. On behalf of the Standards Committee of the British Transplantation Society. Summary of the British transplantation society guidelines for management of the failing kidney transplant. *Transplantation*. 2014;98:1130–1133.
15. Annual organ donation and transplantation activity report 2016/17. NHS blood and transplant. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/4657/activity_report_2016_17.pdf. Updated 2017. Accessed December 26th 2017.
16. Rao PS, Schaubel DE, Jia X, et al. Survival on dialysis post-kidney transplant failure: results from the scientific registry of transplant recipients. *Am J Kidney Dis*. 2007;49:294–300.
17. NHS. Blood and Transplant. Calculators. Tools and calculators in relation to organ transplantation. https://www.odt.nhs.uk/transplantation/tools-policies-and-guidance/calculators/. Accessed September 29th 2017.
18. Tambur AR, Campbell P, Claas FH, et al. Sensitization in Transplantation: Assessment of Risk (STAR) 2017 working group meeting report. *Am J Transplant*. 2018;18:1604–1614.
19. Bayliss GP, Gohh RY, Morrissey PE, et al. Immunosuppression after renal allograft failure: a survey of US practices. *Clin Transplant*. 2013;27:895–900.
20. Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Evolution and clinical pathologic correlations of de novo donor-specific HLA antibody post kidney transplant. *Am J Transplant*. 2012;12:1157–1167.
21. Sellarés J, de Freitas DG, Mengel M, et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. *Am J Transplant*. 2012;12:388–399.
22. Burns J, Cornell LD, Perry DK, et al. Alloantibody levels and acute humoral rejection early after positive crossmatch kidney transplantation. *Am J Transplant*. 2008;8:2684–2694.
23. van der Mast BJ, van Besouw NM, Witvliet MD, et al. Formation of donor-specific human leukocyte antigen antibodies after kidney transplantation: correlation with acute rejection and tapering of immunosuppression. *Transplantation*. 2003;75:871–877.
24. Martin L, Guignier F, Mousson C, et al. Detection of donor-specific anti-HLA antibodies with flow cytometry in eluates and sera from renal transplant recipients with chronic allograft nephropathy. *Transplantation*. 2003;76:395–400.
25. Lachmann N, Schonemann C, El-Awar N, et al. Dynamics and epitope specificity of anti-human leukocyte antibodies following renal allograft nephrectomy. *Nephrol Dial Transplant*. 2016;31:1351–1359.
26. Gloor JM, Winters JL, Cornell LD, et al. Baseline donor-specific antibody levels and outcomes in positive crossmatch kidney transplantation. *Am J Transplant*. 2010;10:582–589.
27. Kassakian CT, Ajmal S, Gohh R, et al. Immunosuppression in the failing and failed transplant kidney: optimizing outcomes. *Nephrol Dial Transplant*. 2016;31:1261–1269.
28. Casey MJ, Wen X, Kayler LK, et al. Prolonged immunosuppression preserves nonsensitization status after kidney transplant failure. *Transplantation*. 2014;98:306–311.
29. Matignon M, Leibler C, Moranne O, et al. Anti-HLA sensitization after kidney allograft nephrectomy: changes one year post-surgery and beneficial effect of intravenous immunoglobulin. *Clin Transplant*. 2016;30:731–740.
30. Hyun J, Park KD, Yoo Y, et al. Effects of different sensitization events on HLA alloimmunization in solid organ transplantation patients. *Transplant Proc*. 2012;44:222–225.