ORIGINAL ARTICLE

Changing patterns of clinical decision making: are falling numbers of antibody incompatible transplants related to the increasing success of the UK Living Kidney Sharing Scheme? A national cohort study

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SUMMARY

Antibody incompatibility is a barrier to living kidney transplantation; antibody incompatible transplantation (AIT) is an accepted treatment modality, albeit higher risk. This study aims to determine changes to clinical decision making and access to AIT in the UK. An electronic survey was sent to all UK renal transplant centres (n = 24), in 2014, and again in 2018. Questions focused on entry & duration in the UKLKSS for HLA and ABO-incompatible pairs, Can and provision of direct AIT transplantation within those centres. Between 2014 & 2018, the duration recommended for patients in the UKLKSS increased. In 2014, 34.8% of centres reported leaving HLA-i pairs in the UKLKSS indefinitely, or reviewing on a case by case basis, by 2018 this increased to 61%. Centres offering direct HLA-i transplantation reduced from 58% to 37%. For low titre (1:8) ABO-i recipients, 66% of centres recommended at least 9 months (3 matching runs) in the UKLKSS scheme in 2018, compared to 47% in 2014, 50% fewer units consider direct ABO-i transplantation for unsuccessful pairs with high ABO titres (>1:512). Over time, clinicians appear to be facilitating more conservative management of AIT patients, potentially limiting access to living donor transplantation.

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Key words
ABO-incompatible, cross-matching, desensitisation, histocompatibility, immunogenetics, kidney clinical, kidney paired donation, live donors

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Introduction

In the field of transplantation, equity of access to transplant is an important consideration [1]. Patients sensitized to Human Leucocyte Antigens (HLAs) by previous transplantation, pregnancy or transfusion comprise a significant proportion of the waiting list for a kidney transplant in both the UK and USA [2,3]. In the UK, registered antibody against HLA antigens is used to derive a calculated reaction frequency, or cRF which refers to the percentage of the last 10 000 UK donors against whom the patient has preformed anti-HLA

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antibody, it may be considered as being approximately equivalent to the calculated panel reactive antibody estimation made in the USA.

Highly sensitized kidney transplant recipients, particularly those with a cRF of> 80% and those of blood group O and B wait longer for a deceased donor kidney transplant in the UK than unsensitized recipients or those of blood group A or AB [3]. In the UK, USA, and Europe, changes to deceased donor organ allocation schemes seek [4,5] to address this imbalance by prioritizing highly sensitized patients [6]

In the UK, for the potential transplant recipient with a living donor who is incompatible - either blood group ABO-incompatible (ABO-i) or HLA-incompatible (HLA-i), the UK Living Kidney Sharing Scheme (UKLKSS) exists to find a suitable compatible match through kidney exchange [7]. The scheme operates on a quarterly basis, and requires strict anonymity [8] between exchanging donor and recipient. Also, all UKLKSS transplants identified within a given matching run should be completed within three 'sharing' weeks, which fall within an eight-week window following the matching run. Since starting in April 2007, the scheme has steadily increased in size [7,9].

In recent years, there have been 4 amendments to the UKLKSS which have resulted in significant changes.

Firstly, since April 2018, the default position for unspecified (altruistic) donors is that they are used to prime 'short' (two kidney transplants) and 'long' (three kidney transplants) donor chains, rather than donate directly to a single waiting list recipient. This has the advantage of ensuring that the increasing numbers of unspecified donor kidneys are used to beneficial effect, as facilitators of donor chains within the UKLKSS which ultimately result in a living kidney donation to someone on the deceased donor waiting list. In 2018, 48% of unspecified kidney donations formed part of a chain in the UKLKSS, compared to 30% in 2017 [10].

Secondly, compatible pairs hoping to improve match characteristics of their living donor (age; HLA mismatch) are increasingly being added to the available pool. Like the addition of unspecified donors to the pool, this has the effect of enriching the matching pool with easier to match recipients, who can unlock new possibilities for exchange.

Thirdly, non-simultaneous transplantation surgery is now permissible in the UK. At the outset of the UKLKSS, all transplants occurring as part of an exchange in the scheme were performed simultaneously; however, there is now an agreed framework for non-simultaneous surgery which assists to facilitate the unspecified donor chains [9].

Finally, an additional change to the UKLKSS permits delisting of unacceptable antigens within the UKLKSS to increase matching principally for those with a calculated reaction frequency (cRF) of> 85% and, to date in the UK, 41 HLA-i transplants have been facilitated in this way.

Nonetheless, despite these changes, for patients who do not achieve a match through the UKLKSS, direct antibody incompatible transplantation (AIT) may be the only option to achieve timely transplantation, but it is unclear how long patients should wait in the UKLKSS for a compatible match, and when they should proceed with an ABO-i or HLA-i transplant.

Our goal with this survey was to assess decision making and access to AIT across all four UK countries, and assess interval changes over a 4-year period with respect to approaches for antibody incompatible recipients, particularly in light of the increased success of the sharing scheme.

Methods

In the UK, identified contacts within the living donor coordination team and H&I (Histocompatibility and Immunogenetics) laboratories associated with each transplant centre are responsible for liaising directly with the UKLKSS coordinators at NHSBT to register eligible donor-recipient pairs into the scheme, confirm their inclusion before each matching run and all clinical and scientific information up-to-date.

In conjunction with NHS Blood & Transplant (NHSBT), an electronic survey was developed and disseminated to all UK renal transplant centres (n = 24), through lead clinicians, heads of H& I laboratories and living donor nurse coordinators. The survey was sent on two different occasions: firstly in 2014 to establish practice, and then again in 2018 following changes to the UKLKSS. As a survey of current clinical practice, ethical approval was not required.

Respondents were questioned about entry into the UKLKSS, criteria for exit from the scheme for unmatched recipients, whether or not direct ABO-i or HLA-i was offered and protocols for such transplants, as well as local H & I laboratory practice. In this survey, crossmatch positive is taken to mean 'crossmatch positive by CDC and/or Flow Cytometry' as decided by the local laboratory standards, and consistent with their reporting to NHSBT & the UK transplant registry.

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Results were analysed in two ways – by respondent and by centre. For centre responses, if a difference of response was noted between respondents, then the opinion of the clinical lead was accepted as being the representative response. Additional data regarding the UKLKSS was provided by NHSBT.

Results

A total of 80 respondents took the survey in 2014, and 77 in 2018, covering all 24 (100%) renal transplant centres in the UK (23 adult units & 1 paediatric unit). 38% of respondents were clinicians (physicians or surgeons), 23% H&I scientists & 39% specialist nurses.

HLA-incompatible transplantation

In 2014, 16 centres (66%) offered transplantation for crossmatch positive HLA-i living donor transplant recipients. Of the 8 centres who did not offer crossmatch positive transplantation, two had no pathway for referring patients on for crossmatch positive transplantation at another centre. By 2018, only 12 (50%) of units offered cross match positive HLA-i living donor transplantation. The reasons given for not offering direct HLA-i related to low volumes of such transplants, and concerns regarding the outcomes.

The NHSBT definition of HLA-i transplantation includes patients who are crossmatch negative by CDC or Flow Cytometry but DSA positive by Luminex.

In 2013-14 calendar year, HLA-i comprised 53 living donor (LD) transplants in the UK, of whom 31 were FXCM & DSA + ve, and 14 were DSA + ve (FXCM negative) only, with 8 not reported or unknown. By 2017–2018, this number fell to 20 HLA-i LD kidney transplants undertaken, (see Fig. 1) of whom 5 were FXCM & DSA + ve, 1 was DSA + ve, and 14 were unknown or unreported, (www.odt.nhs.uk, updated calendar year transplant numbers, personal correspondence, Matthew Robb, NHSBT).

In 2014, 21 (87.5%) UK renal transplant centres, performed crossmatch negative, DSA positive transplants without additional antibody removal therapy, however, only 45.8% (11 centres) registered them as HLA-i with NHSBT. By 2018, although changes were discussed, the current definition remains, and DSA positive, crossmatch-negative transplants may be registered with NHSBT as HLA-incompatible. From our survey, it is evident that only some centres register the transplants in this way; nonetheless, due to lack of reporting, the transplant data lack clarity as to whether there really are proportionally fewer FXCM positive transplants occurring with time.

Protocols across centres vary, the majority of centres reported using depletional agents (Anti- Thymocyte Globulin (ATG), Alemtuzumab) for complement dependent cytotoxicity (CDC) or Flow cross match (FXCM) positive patients receiving desensitization. Some centres (n = 2) use Basiliximab (IL-2 inhibitor), while one centre reported use of Rituximab. In 2018 only two centres

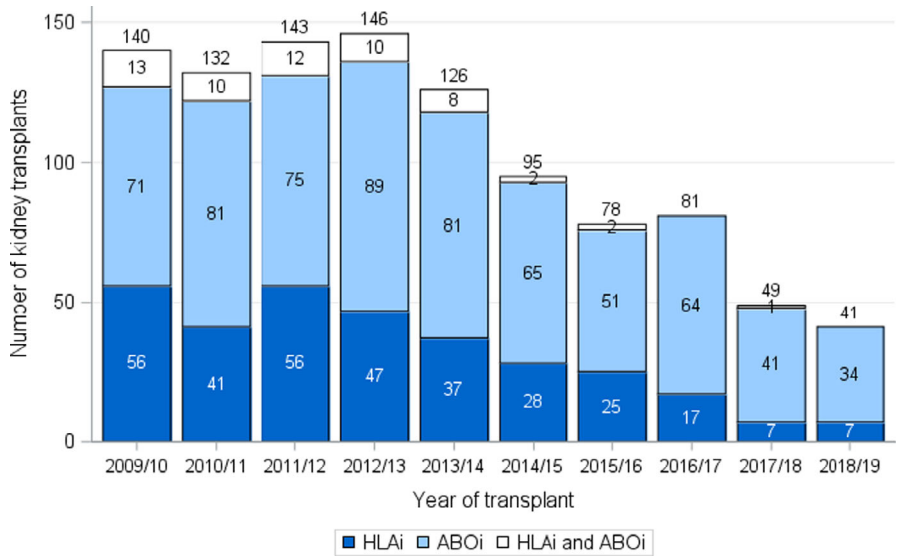

Figure 1 Adult living donor antibody incompatible transplants in the UK, 1 April 2009 – 31 March 2019, source www.odt.nhs.uk. Note, fiscal year reporting of official statistics, while manuscript reflects calendar year reporting which includes late notifications.

reported having access to funding for rescue Eculizumab for use in HLA-i transplants.

ABO-incompatible transplantation

ABO-i transplantation is offered by 23 of the 24 (95.8%) renal transplant centres in the UK, including two paediatric centres linked to the same adult centre. In 2014, ABO-i transplantation accounted for between 5-7% of adult LD kidney transplants per year (www.odt.nhs.uk). 2008 was the most popular year for centres to start performing ABO-i, with the earliest adopting units reporting starting ABO-i in 2004. The single centre not offering direct ABO-i transplantation in 2014 implemented plans to introduce a protocol by 2018, while a centre which had previously undertaken ABO-i during the initial survey no longer offered this modality in 2018.

In 2014, for many centres (39%), 1:512 was the highest baseline ABO-i titre considered for direct ABO-i transplantation, while only 1 centre reported that there was no limit on baseline ABO antibody titre. 17 centres reported 'acceptable' ABO titres on the day of transplant: for 11 (64% of reporting centres; 50% of ABO centres) the 'acceptable' ABO titre on the day of transplant was 1:8; 4 centres reported that ABO titres on the day of transplant should be 1:4; 2 centres reported that this was decided on a case by case basis.

Over time, the range of baseline acceptable ABO titres are decreasing, suggesting a more conservative approach to ABO-incompatible transplantation. In 2018, 40% of centres reported that 1:128 would be the highest baseline ABO-i titre considered for direct ABO-i transplantation, while the number of centres accepting baseline titres of 1:512 was halved to 20% of centres.

Treatment protocols for ABO-i transplantation vary by centre, although the majority of centres (82.6%) offer Rituximab treatment. 6 centres (26%) centres offer immunoadsorption (IA) treatment in addition to double filtration plasmapheresis (DFPP) but 10 centres (43%) offer DFPP alone as antibody removal method of choice. 6 centres offer low dose intravenous immunoglobulin (IvIg) therapy for patients undergoing ABO-i, and 1 centre offers high dose IvIg treatment.

Multidisciplinary management of AIT patients

In 2014, 75% (18) of renal transplant centres reported that they offered a dedicated multidisciplinary team meeting (MDT) to discuss AIT options for patients – comprising clinicians, H & I scientist and living donor nurse/s. The reported frequency of such meetings was weekly 22%; fortnightly 22%; monthly 44%, the remainder (12%) meet around the time of the UKLKSS matching run (quarterly), In 2018, the use of MDT meetings to discuss AIT patients was more widespread, with only 2 centres reported not having a dedicated MDT to discuss AIT patients.

Paired/pooled Donation Scheme

The UKLKSS includes the paired (2-way exchanges)/pooled (3-way exchanges) donation (UKLKSS) scheme and matching runs occur quarterly, administered by NHS Blood and Transplant (NHSBT) using a bespoke algorithm developed with colleagues at Glasgow University. From inception in 2007 to 2018, there have been 1874 patients registered in the scheme, with 842 patients transplanted. As with other sharing schemes, the pool has accumulated highly sensitized patients, in total 42% of the pool of registered patients have a cRF of > 85%. During 2014, the total number of patients included in the matching runs was 329, with 72 patients receiving a transplant via the UKLKSS, or 8.2% of LD kidney transplants. Of the 250 untransplanted patients, 64% had a cRF of 85% or greater. In 2014, 36% (n = 28) of the patients transplanted through the UKLKSS scheme had a cRF of > 85%, see Table 1.

By 2017/18, the numbers of pairs registered for each run was around 200, and the number of transplants completed in the year had increased to 123, forming 13% of LD kidney transplants. Of the 365 patients included in matching runs but not transplanted, 52% had a cRF of 85% or greater. In 2018, the proportion and number of patients transplanted through the UKLKSS scheme with a cRF of 85% or greater had decreased to 24% (n = 25), see Table 1.

Table 1. Calculated reaction frequency (cRF) of patients transplanted through the UKLKSS during the calendar years 2014 & 2018

	Number (%) of patients	
	2014	2018
cRF		
0-9	29 (37.6%)	65 (44.5%)
10-49	5 (6.5%)	19 (13.0%)
50-84	15 (19.5%)	27 (18.5%)
85-94	9 (11.7%)	20 (13.7%)
95-100	19 (24.7%)	15 (10.3%)

This does not include listed patients at the end of chains who received a transplant via the UKLKSS.

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Attendant with the increase in transplants through the UKLKSS there has been a reduction in the number of direct ABO-i & HLA-i transplant in the UK from 85 direct ABO-i and 53 HLA-i in the finalized calendar year reporting of 2014 to 41 direct ABO-i and 20 HLA-i occurring in the UK in the finalized calendar year reporting of 2018 (personal correspondence, Matthew Robb, Lead Kidney Statistician, NHSBT) see Fig. 1 (www.odt.nhs.uk) for financial year transplant numbers, published ahead of final calendar year reporting [9].

In 2014, 3 centres (12.5%) reported not having a named clinician responsible for registration of suitable donor-recipient pairs into the scheme, only one (4%) centre reported not having a named nurse. In 2018 this number of centres without a named clinician increased to 4 centres (16.7%).

Regarding the testing of baseline ABO titres before entry into the UKLKSS for ABO-incompatible pairs, there was no change between 2014 and 2018: 79% of centres undertake baseline testing. Of the 5 centres that do not test baseline titres before UKLKSS entry, 1 centre does not offer direct ABO-i transplantation in centre and, therefore, may not have easy access to laboratory facilities for routine ABO titre measurement. Of the centres that offer ABO-i transplantation, in 2014 75% would potentially offer direct ABO-i transplantation without entry into the UKLKSS scheme first, depending on baseline ABO-antibody titre. In 2018, this was essentially unchanged with 17% (4) centres still reporting that they do not check ABO antibody titres prior to entry into the UKLKSS.

Regarding the decision of when to remove patients who have failed to find a successful match in the UKLKSS scheme, for ABO-i pairs, baseline ABO titres affected outcome. In 2014, 53% of centres reported offering a direct transplant after 1 failed run in the UKLKSS for patients with a starting ABO antibody titre of 1:8, this percentage fell to 33% for baseline titres of 1:64, and 10.5% for baseline titres of 1:512. One third (33%) of centres reported that patients with baseline titres of 1:512 would be left in the UKLKSS indefinitely.

In 2018, centres reported being more likely to leave ABO-i pairs longer in the scheme if their baseline titres were higher (>1:64), while 50% of centres reported they would leave ABO-i pairs with a baseline titre of> 1:512 in the UKLKSS indefinitely, see Table 2.

For HLA-i recipients in 2014, over half of the centres advised patients to remain in the UKLKSS scheme for between 9–12 months (3–4 runs), while 17.4% of centres recommended that patients remain in the UKLKSS indefinitely. 15 centres (62.5%) reported that they had 'delisted' antibody specificities for HLA-i pairs in the UKLKSS to increase the chance of obtaining a match. In 2018, half of centres reported that for HLA-i patients unsuccessful in obtaining a match through the UKLKSS, the decision to consider a direct HLA-i transplant was a decision made on a case by case basis, while no centres would withdraw HLA-i patients from the scheme unless they had spent at least a year in the UKLKSS, see Table 3.

Interestingly, in 2018, 83% of units reported using extended criteria profiles to 'delist' HLA antigen specificities when registering UKLKSS patients, according to antibodies that may be deemed to be transplantable either with or without additional desensitization treatments. This practice is used by some UK centres for patients on the deceased donor list [11], but in this setting permits for different unacceptable antigen profile to be registered on the deceased donor list, compared to the UKLKSS, thus increasing the pool of potential donors within the scheme. 22% of centres reported using desensitization together with the UKLKSS, while a further 22% reported being prepared to consider this type of transplant. Additionally, in 2018, 22 of the 24 (92%) centres report entering compatible pairs into the UKLKSS.

Table 2. Recommended duration in the UK NLDKSS for ABO-incompatible pairs for a given baseline anti-ABO antibody titre at a. 1:8 anti-ABO titre (low); b. 1:64 anti-ABO titre (intermediate); c. 1:512 anti-ABO titre (high)

	1:8		1:64		1:512	
	2014	2018	2014	2018	2014	2018
1 matching run (3 months)	53%	33.3%	33%	5.8%	10.5%	0%
3 matching runs (9 months)	32%	33.3%	39%	53.5%	26.5%	17.5%
4 matching runs (1 year)	5%	22%	17%	35.4%	26.5%	23.5%
Indefinitely	0%	5.5%	0%	5.8%	31.5%	55%
Decided on a case by case, basis according to patient preference	10%	5.5%	11%	0%	5%	0%

Table 3. Recommended duration in the UK NLDKSS for HLA-incompatible cross match positive pairs by unit

	2014	2018
1 matching run (3 months)	13%	0%
3 matching runs (9 months)	30.5%	0%
4 matching runs (1 year)	21.7%	33%
8 matching runs (2 years)	0%	5.5%
Indefinitely	17.4%	11%
Decided on a case by case, basis according to patient preference	17.4%	50%

UKLKSS pool composition 2014–2018

In 2014, the UKLKSS pool comprised 329 recipients, of whom 250 remained untransplanted by the end of the year (4 matching runs). Of those remaining, 54 patients (21.6%) had a cRF of 0–9%, while 160 (60%) had a cRF of> 85%. 56% of patients appeared in 4 or less matching runs, while 79% of the patients remaining in the pool had been in the pool for 8 or less runs, with a median of 4 matching runs per patient (equivalent to 1 year). In 2018, the total number of patients included in the UKLKSS was 517, of whom 365 remained untransplanted. Of the untransplanted group, compared to 2014 a larger proportion (27.4%, $n = 100$) had a cRF of 0-9%, while a lesser proportion (52.3%, $n = 191$) had a cRF of> 85%, consistent with the pool expanding as a result of compatible pairs being added, and the relative proportions of highly sensitized patients reducing, despite numbers being high. With the pool enriched for less sensitized patients, there is evidence that patients are being matched more quickly with a larger proportion of unmatched patients (68%) in the pool for less than 4 matching runs (1 year), and 83% featuring in 8 or less matching runs, with a median of 3 matching runs, (personal correspondence, Matthew Robb, Lead Kidney Statistician, NHSBT).

Respondent comments

In 2018, 61% of respondents reported that their own listing practices for UKLKSS entry and exit had changed since 2014. Respondents were also asked to give free text responses to questions on what they considered to be the reasons driving this change of practice over the 4-year interval of the study, as well as future changes they wished to see. With respect to the changes to their practice over time, in 2018 many respondents felt that the increased pool size and chance of success relating to the UKLKSS, in combination with observation of poor clinical outcomes after HLA-i had overall served to confine HLA-incompatible transplantation to a small number of specialist centres. A common theme with respect to future changes was the request for UK standardization of both clinical protocols and funding tariffs for HLA-i and ABO-i transplantation. Many respondents spontaneously reported 'equity of access' to transplantation as being a key concern when considering the transplant options for antibody incompatible patients in the UK. In addition, several respondents requested a greater cohesive research strategy, as well as access to obtaining, and research related to the role of, Eculizumab and, more broadly, UK outcomes in AIT.

Discussion

This paper sets out the practice of AIT in the UK in 2014 and the changes that occurred by 2018.

We observe that over a relatively short 4 year period, there has been both an increase in the number of transplants completed through the UKLKSS, as well as a dramatic fall in AIT transplant numbers [9]. More centres are offering dedicated MDT fora to discuss AIT patients; however, patients are more likely to be recommended to wait longer, or even indefinitely in the UKLKSS in 2018, compared to 2014. The addition of compatible pairs is gaining traction as a means of enriching the UKLKSS pool with easy to match patients, with the goal of achieving more transplants, and is demonstrably reducing the proportion of patients with a cRF of> 85%. With respect to patients who are unsuccessful in the UKLKSS, fewer centres are offering direct HLA-incompatible transplantation in 2018, compared to 2014, while direct ABO-i transplantation in 2018 is mainly being offered to pairs with a lower baseline ABO antibody titre, who are perceived to have a lower immunological risk. Our data suggest that, over the past 4 years, a more conservative approach towards AIT has become more prevalent.

Dedicated clinicians and a multidisciplinary team (MDT) discussion about patients is standard clinical practice in the UK in many specialities. Between 2014 and 2018, it has become evident that more transplant centres have adopted this practice. As the data from the survey show, for the majority of antibody incompatible patients, this occurs at least monthly; however, in 10% of centres, this occurs less frequently, (4 times per year). Compared to other national, regional and single centre kidney paired donation (KPD) programmes, the UKLKSS has relatively infrequent matching runs [7,12-

14], in part this is to allow the pool size to increase before matching run. This is one explanation for the infrequent review of antibody incompatible patients; however, the decision making process and likelihood of timely transplantation may be improved for a patient who is discussed at a more frequent dedicated meeting, compared to a 3 monthly meeting since there is opportunity for more nuanced discussions related to dialysis quality, patient frailty and ability to withstand additional immunosuppression, patient risk perception and life quality, as well as options such as: alternative living donors; suitable antigens to be delisted either for greater matchability; consideration of combination HLA with the UKLKSS to be explored with the patient in clinic, pending the outcomes from the next UKLKSS matching run.

Data from NHSBT suggest that if a patient has been unsuccessful in obtaining a match in the UKLKSS within 4- 5 matching runs, then success is unlikely [15] although with increasing numbers of altruistic donors, this is changing all the time. Additionally [15], as presented, the UKLKSS pool has a high number of patients with a calculated reaction frequency (cRF) of> 85%, although the proportions of minimally sensitized patients are becoming greater [9]. From the respondent comments, it seems that in 2018, highly sensitized patients are more likely to be left indefinitely in the UKLKSS due to clinician concerns regarding patient and graft outcomes from direct transplants. While such concerns regarding the risks of complications of treatment for direct HLA-incompatible transplantation are justified, undertaking very small numbers of HLA-incompatible transplants in a year within the UK, suggests the potential for an untransplanted group of patients who have a living donor, but are not being offered direct HLA-i transplantation. In the only UK-wide analysis of patient and graft survival in a matched cohort of sensitized recipients, comparing proceeding with an HLA-incompatible transplant to awaiting a compatible alternative, 41% remained untransplanted at 58 months. Our data at that time also showed that for sensitized patients in the control cohort, those who were registered for less than 12 months (4 runs) in the UKLKSS from the date of matching had an increased rate of achieving living donor compatible transplant, than those who had already been in the UKLKSS for more than 4 runs [16], suggesting that the best chance of successful matching occurs within the first year of registration in the UKLKSS. Our approach is to advocate for ongoing discussions between clinician and patient over the course of 4 runs spent in the UKLKSS, in order to gauge whether the increased risk of rejection and treatment side effects is something that the patient wishes to consider, in the context of the patient's own quality of life on dialysis. As the patient spends increasing time in the pool, they should be counselled that the chance of a compatible match decreases.

For patients with ABO-i donors, the variation in approach is most marked. Direct ABO-i transplantation has been widely recognized as offering good transplant outcomes [17], yet low numbers of centres in USA offer this modality [18]. Detractors state that this transplant modality is more expensive, and less effective than compatible transplantation [19]. However, for some patients, ABO-i transplantation is possible without antibody removal [20], and minor ABO-incompatibility has been used as a means of increasing deceased donor allocation of organs to blood group B recipients [21]. It is, therefore, surprising that 20% of centres do not screen ABO titres prior to entry into the UKLKSS. Additionally, 25% of reporting centres stated that they would not allow direct ABO-i transplantation to proceed without an initial period in the UKLKSS scheme, irrespective of starting ABO titres. We concur with the latest UK living Donor Kidney Transplant Strategy group recommendation that ABO antibody titre measurement should be a routine part of an assessment about the risk/benefit of waiting for a compatible transplant, compared to undertaking a direct ABO-i which, if low titre, requires no additional treatment. However, there are occasions in which either due to patient preference to avoid the sharing scheme, clinical urgency, or a low predicted success rate as a consequence of the pair combination [9], the first choice option for a patient may be direct ABO-incompatible transplant.

Further evidence of risk aversion amongst clinicians with respect to direct ABO-i is evidenced by the reduction of acceptable baseline ABO antibody titres prior to consideration of a direct ABO-i over time. By contrast to the situation in the USA, ABO-i transplantation in the UK is offered more widely than HLA-i; however, the difference over time in willingness to undertake higher baseline titre of ABO antibody, as well as 'cut-offs' for ABO titres on the day of transplantation is marked (Table 3). Making global comparisons across titre measurements is challenging due to the difference in testing methodologies and lack of standardization; however, it should be noted that acceptable titres on the day of transplant vary. In Japan, acceptable titre measurements for the day of transplant range from 1:16 to 1:32, while in Sweden they are 1:4, but as a consequence of this 14-21% of patients fail desensitization [22].

However, it should also be considered that the relationship between high baseline titre predicting immunological risk in ABO-incompatible transplantation, is not well defined, in a comparison of high baseline titre (>1:256+), compared to low (<1:128), Chung et al demonstrated no difference in antibody mediated rejection rates between groups, although the high titre group experienced more infectious side effects of immunosuppression in a protocol in which the aim was a pre-transplant titre of 1:32 [23].

Undoubtedly, there are differences of local laboratory titre measurements which make interpretation of these self-reported ABO antibody titre cut-offs difficult across transplant centres [24]. In the UK there are plans for standardization of ABO titre measurements and methodologies. Alternative, more sensitive flow techniques have been recommended for some time [25], and solid phase assays are in development but these techniques await validation and widespread adoption. Nonetheless, it remains the trend that lower acceptable baseline titres for ABO-incompatible transplantation in 2018, compared to 2014, may explain the falling numbers of direct ABO-incompatible transplants.

It is evident from the free text comments by respondents that professionals involved in AIT share concerns about centre differences in approaches to AIT in the UK, as well as concerns about the perceived immunological risk that direct HLA-i or ABO-i transplantation represents. The Access to Transplantation and Transplant Outcome Measures (ATTOM) study of patients in the UK highlighted the quantitative and qualitative areas of inequality in access to transplantation [1,26–28]. It is incumbent upon all those involved in AIT to ensure that practice across the UK with respect to entry and exit from the UKLKSS and decision making regarding AIT is standardized, informed and up-to-date in order to ensure that all suitable patients in the UK have the same access to consideration of AIT, if this is what the patient wishes.

Inevitably, a limitation of this study is the heterogeneity of approach that is evident, and the difficulty of comparing immunological risk across 24 units and their associated Histocompatibility & Immunogenetic (H & I) laboratories. In the UK, most centres perform flow cytometry cross matching 'in-house' and determine their own thresholds for positivity. Despite national standardization by the UK National External Quality Assessment Scheme for H&I (UK NEQAS), it seems likely that clinicians may best be able to appreciate the immunological risk based on tests performed by their own laboratory. Not only are testing strategies difficult to compare but, clearly there is variation with respect to the desensitization protocols and timing of direct AIT after UKLKSS scheme entry. Nomenclature relating to AIT is not standardized, neither are methodologies for testing for ABO antibody and positive cross match thresholds [24]. Additionally, there is variation in desensitization protocols for AIT [29–32]. It is likely that this variation relates to complex decision making by individual patients and their clinicians, particularly as the options for kidney paired donation and AIT evolve [33–35]. Fortunately, the tighter definitions of HLA-i within the UK to exclude DSA positive, cross match negative transplants appear to be accepted, and in keeping with earlier practice demonstrated in 2014.

This survey provides an important snapshot of UK practice over a four-year period which demonstrates subtle but significant changes to practice. Many of the responses reveal that the approach to such patients is personalized, which has an impact on understanding outcomes from individual centres. The observed changes over such a short period of time in clinical practice reflect an increasingly successful UKLKSS, which is laudable, but the wide variation in practice with respect to patients who are unsuccessful in achieving a match through this scheme suggests the possibility of a waning risk appetite of clinicians. For many patients, this decline in clinician willingness to undertake incompatible transplantation may be appropriate, and in keeping with evidence to suggest no survival benefit for patients undergoing HLA-i in the UK; however, this approach may risk leaving highly sensitized patients untransplanted. A new allocation system in the UK, which increases the prioritization of deceased donor organs to benefit sensitized patients is likely to improve compatible allocation, as it has in the USA. Nonetheless, despite improved access to compatible deceased donor transplantation, as Schinstock et al demonstrate, there is a need to consider the patients for whom these allocation changes are not enough [36]. It is evident from these data that individualized decision making for AIT patients is more prevalent, which is good, the challenge is to ensure that this is appropriate, and not reducing access to transplantation for patients willing to undertake greater risk than their clinicians. We advocate a 'hub & spoke' model in which smaller number of specialist centres offer highly specialized direct antibody incompatible transplantation for those patients for whom alternatives paths to transplantation have failed.

Authorship

MM & NM conceived the idea, and co-wrote the survey with LB & SF, with input from RJ. All authors were involved in research design. LB assisted MM in

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disseminating the survey. MM analysed the results, and wrote the initial draft of the manuscript. All authors contributed to revisions and conclusions.

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