ORIGINAL ARTICLE

For the many: permitting deceased donor kidney transplantation across low-titre blood group antibodies can reduce wait times for blood group B recipients, and improve the overall number of 000MM transplants - a multicentre observational cohort study

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SUMMARY

Blood group O or B recipients wait longer for a kidney transplant. We studied the distribution of anti-ABO blood group antibody titres in patients awaiting a kidney transplant, and modelled the effect of altering the UK National Kidney Allocation Scheme to allow for patients with 'LOW' titres (≤1:8, ≤3 dilutions) to receive a deceased donor ABOi (ddABOi) transplant. In a prospective study of 239 adult patients on the waiting list for a transplant in 2 UK centres, ABO-antibody titres (anti-A and anti-B) were measured. Based on the proportions of 'LOW' anti-A or anti-B antibodies, four simulations were performed to model the current allocation rules compared with variations allowing ddABOi allocation under various conditions of blood group, HLA matching, and waiting time. The simulations permitting ddABOi resulted in more blood group B recipients being transplanted, with median waiting time reduced for this group of recipients, and more equitable waiting times across blood groups. Additionally, permitting ddABOi resulted in greater numbers of 000MM allocations overall in compatible transplants under modelled conditions. Changing allocation in the UK to permit ddABOi in patients with 'LOW' titres would not change the total number of transplants, but redistributes allocation more equitably amongst blood groups, altering waiting times accordingly.

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Introduction

Globally, ABO blood group antibody incompatible (ABOi) transplantation has become an accepted option for renal transplantation between blood group incompatible living donor pairs, although uptake in the USA remains low. Long-term outcomes are very good, with 1 year graft survival of 96% reported in a large meta-

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analysis [1]. Increasingly, treatment protocols are tailored based on antibody titres, with many centres reporting minimal pretransplant antibody removal in recipients with titres of blood group antibodies of 1:8 or lower [2–4], as well as the minimization of the use of rituximab. However, despite advances in opportunities for living donor pairs to address donor–recipient incompatibility with ABO-incompatible transplantation, there is disparity in waiting times between patients of different blood groups on the deceased donor waiting list. European studies show a 'blood group O' problem of recipients accumulating on the deceased donor transplant list, [5]. In the UK, adult patients on the waiting list for a kidney transplant with blood group O or B have significantly longer waiting times than patients of blood group A or AB [6], with a similar finding in the USA [7].

In the modern era, ABOi kidney transplantation is primarily considered to be a transplant option for living donor pairs, despite some early reports of deceased donor ABOi (ddABOi) success [8,9]. There have long been advocates for transplantation of kidneys from A2 donors into ABOi deceased donor recipients, since the expression of A2 antigen on the endothelium is limited and kidneys are assumed to 'act' like a blood group O kidney [10]. However, clinical exploitation of this phenomenon has been limited - in a retrospective analysis of A2 kidney use in the USA, it was found that only 15% of the possible A2 allografts had been allocated to O or B recipients [7]. Nonetheless, the recent changes in the US Kidney Allocation Scheme (KAS) allow A2 to B or O allocation and demonstrate improved rates of transplantation for Blood Group B recipients, albeit with little of the predicted effect on rates of transplantation for ethnic minorities [11,12]. Centres for liver and infant heart transplantation, by necessity because of organ shortage, have developed a practice of ddABOi transplantation [13–15].

In the paediatric renal population, we have proposed ddABOi transplantation for low-titre recipients [16]. Despite strong advocates for this transplant option [17], this has not yet, to our knowledge, happened in the UK – perhaps because of the relatively high priority of children within the national allocation system making the need for this type of transplant limited.

Although the distribution of ABO blood group antibody titres has been reported in a number of studies of adult ABOi renal transplantation it has not previously been measured in an unselected adult population representative of the deceased donor waiting list [18–20]. The goal of this study was to test the distribution of ABO antibody titres in the population of adult patients awaiting a renal transplant. Having established the distribution of ABO-antibody in the population of patients on the waiting list for a kidney transplant, we then assessed the feasibility of allocating ABOi kidneys to patients with sufficiently low ABO antibody levels (requiring no pretransplant antibody removal), and modelled the effect on transplant rates and waiting times of permissive ABOi transplantation through the UK national deceased donor kidney allocation system (UK NKAS), based on the accepted ABO-antibody levels (ABO titres of $\leq$1:8) agreed by UK transplant centres.

Methods

This prospective observational study of adult patients on the deceased donor renal transplant waiting list was approved locally, and nationally by the National Research Ethics Committee (REC 12/EM/0478). Following informed consent, a routine blood sample was used to exclude atypical antibodies. In patients with a negative atypical antibody screen, Anti-A and anti-B antibody titres (total immunoglobulin load) were measured by the Indirect Antiglobulin Test (IAT) using gel cards (DiaMed ID-Card Coombs anti-IgG, catalogue number 004025) in a single laboratory (GSTS Pathology, St Thomas' Hospital, Westminster Bridge Road, London, SE1 7EH). Medical records were accessed for demographic information, transplant and medication history, and linked to the UK Transplant Registry held by NHS Blood and Transplant. All ABO titres are reported as a dilution, which transforms the logarithmic titre values to a linear scale. ABO antibodies of 1:2 are therefore 1 dilution; 1:4 are 2 dilutions, 1:8 is 3 dilutions etc.

Statistical power was based on the estimated blood group frequencies and proportions of the London population (NHS Bloodstocks management scheme, Table 1), and a precision of 0.15 (15%). We planned to detect 143 anti-A titre measures and 169 anti-B titre measures assuming the measures are normally distributed with a 95% confidence interval of 0.15 to detect a population proportion of 30% for anti-A titre and a population proportion of 45% for anti-B titre, and therefore powered our study to recruit 239 patients.

Simulations

Four simulations were performed; each represents 4 years of kidney transplant activity. Estimations of 'proportions of patients with 'LOW' titres were applied at the start of the simulation, as well as subsequently

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Table 1. Proportions of ABO Blood group distribution amongst the general population in London & England, compared to the study cohort, (expected proportions from NHS Bloodstocks Management).

	O Anti-A & Anti-B	A Anti-B	B Anti-A	AB
Expected London proportions	44.9%	35.5%	15.1%	4.5%
Expected England proportions	45.5%	28.7	11%	3.7
Recruited proportions (*n*)	43% (123)	29% (69)	17% (41)	2% (5)
Titre tested proportions (*n*)	55.4% (108)	28.7% (56)	15.5% (31)	n/a

listed patients. A baseline (BASELINE) simulation provides a representative estimation of the current UK NKAS [21]. Under the terms of the 2006 NKAS [21], all Donation after Brainstem Death (DBD) kidneys are allocated according to restricted blood group compatible matches – see Table 2. In the UK, transplant allocation is tiered, with paediatric recipients receiving priority. Thereafter a weighted combination of HLA matching, waiting time, and donor–recipient age factors are pooled. Adult Tiers are C-E with Tier C being 000 mismatched grafts; Tier D favourably matched & Tier E representing the least well-matched. HLA Levels are as following: Level 1 (000 mismatch); Level 2 (0DR 0/1B MM); Level 3 (0DR 2B MM) or (1DR 0/1B MM) [21].

Simulation 1 (SIM1) allows adults with 'low' anti-A or anti-B to receive an appropriate ABOi donor, if available. In one of the runs 'LOW-TITRES the permissible ABO titre for ABOi allocation was ≤1:8 or a dilution of ≤3. *Simulation 2* (SIM2) is as for SIM1, but only allows kidneys from blood group B donors to be allocated to blood group A adults, if they are zero (000) HLA-mismatched with a given donor. *Simulation 3* (SIM3) is as for SIM1, but only allows kidneys from blood group B donors to be allocated to blood group B adult recipients. The restrictions for SIM 2 & 3 are specifically designed to prevent increased waiting times for blood group B recipients. *Simulation 4* (SIM4) operates under the same allocation rules as SIM1 but restricts the allocation of ABOi kidneys to 'LONG-WAIT' recipients who have been waiting at least 7 years. For tabulated descriptions, please see Supplementary Table 1.

Comparison of baseline characteristics was performed using SPSS 22.0.

Table 2. Current UK National Kidney allocation scheme donor-recipient blood group matching policy (BASELINE).

	Recipient			
Donor	O	A	B	AB
O	✓	✓*	✓	✓*
A	–	✓	–	✓
B	–	–	✓	✓*
AB	–	–	–	✓

–, Blood group incompatible, not matched.

*000 mismatched very highly sensitised (cRF ≥95%) adult patients & 000 mismatched paediatric patients only.

Results

A total of 239 patients were recruited to the study between October 2013 - April 2015 from two UK hospitals, and their attendant dialysis units (Guy's & St Thomas's Hospital & King's College Hospital, London). The analysis and modelling was based on ABO-antibody titre samples obtained in a total of 195 patients, comprising: 108 blood group O (55.4%); 56 blood group A (28.7); 31 blood group B (15.9%), which was comparable with expected proportions for London, Table 1. Of the withdrawals from analysis: five patients who were blood group AB were recruited, on whom no titres were tested, four (three blood group O; one blood group B) patients with atypical antibodies were also not included, the remaining 35 patients either withdrew consent, or had a change in transplant status, resulting in introduction of immunosuppression, before samples could be analysed. A total of 164 anti-B and 138 anti-A measurements were made, resulting in a precision of with a 95% CI.

Demographics of patients in the modelling cohort

The demographics of the sampled cohort of 195 adult patients awaiting a kidney transplant by blood group are shown in Table 3. Candidates were similar by age at registration and dialysis modality. Like other studies [15], there was a notable difference in ethnicity by blood group, with most blood group A patients being white. Blood group A patients had, on average, been listed for less time than the blood group B and O patients (median, range: A: 629, 1–7913 vs. B: 767, 10 –

Table 3. Demographic characteristics of the patient cohort used for modelling purposes.

	Blood group		
	O *n* = 108 (55.4%)	A *n* = 56 (28.7)	B *n* = 31 (15.5%)
Median age at registration, years Median (range)	48 (19–71)	47.2 (23–71)	48.1 (27–70)
Female	32.4%	41.1%	51.6%
Race			
Asian	11.1%	5.4%	13.3%
Black	52.8%	39.3%	56.7%
White	28.7%	51.8%	26.7%
Other	7.4%	3.6%	3.3%
Number of previous transplants			
None	66.7%	67.9%	80.6%
1	28.7%	26.8%	16.1%
>1	3.6%	5.4%	3.2%
Dialysis modality			
Haemodialysis	70.4%	67.3%	72.4%
Peritoneal Dialysis	24.1%	12.7%	6.9%
Predialysis	5.6%	20%	20.7%
cRF – current, median (range)	51.0% (0–100%)	66.0% (0–100%)	5.0% (0–100%)
0%	36.1%	30.2%	44.8%
1–64%	21.3%	18.9%	27.6%
65–84%	11.1%	7.5%	13.8%
85–100%	31.5%	43.4%	13.8%
cRF at registration median (IQR)	28% (89%)	66.0% (98.5%)	4% (48.5%)
0%	42.6%	35.2%	50.0%
1–4%	20.4%	25.9%	26.7%
65–84%	18.5%	9.3%	6.6%
85–100%	18.5%	27.8%	26.7%
Time on waiting list, days median (range)	717 (119–5228)	629 (1–7913)	767 (10–2530)
'LOW' Anti-A ab Dilution ≤3 (*n*)	0	–	32.2% (10/31)
Anti-A ab Dilution ≤6 (*n*)	25.2% (27/108)	–	96.7% (30/31)
'LOW' Anti-B ab Dilution 3 (*n*)	7.4% (8/108)	64.3% (36/56)	–
Anti-B ab Dilution 6 (*n*)	50% (54/108)	98.2% (55/56)	–

2530 & O: 717, 119–5228) but this was not significant. Most blood group B patients had not previously received a transplant (80.6%). The proportion of blood group A patients with a cRF (calculated reaction frequency) of 0% was 30.2%; lower than either blood group B 44.8% or blood group O 36.1%. Despite this, 43.4% of blood group A patients sampled had a cRF of >85% (blood group B 13.8%; blood group O 31.5%).

Distribution of anti-A and anti-B antibody by blood group

Distribution of measured anti-A and anti-B antibody dilution in the modelled cohort are shown in Fig. 1. Of note, blood group O recipients had significantly higher anti-A antibody (median anti-A antibody dilution, 8, IQR 3) than blood group B patients (median anti-A antibody dilution 4, IQR 2), which was statistically significant ($P < 0.05$) and anti-B antibody levels (median blood group O Anti-B dilution 6 IQR 3) than blood group A patients (median blood group A Anti-B dilution 3, IQR 2) ($P < 0.05$). This was reflected by the proportion of the cohort who met the criteria for 'LOW' levels; there were no blood group O patients who had 'LOW' anti-A antibody levels, compared with 9.7% of the blood group B patients. Amongst blood group O patients, there was a strong correlation between anti-A and anti-B

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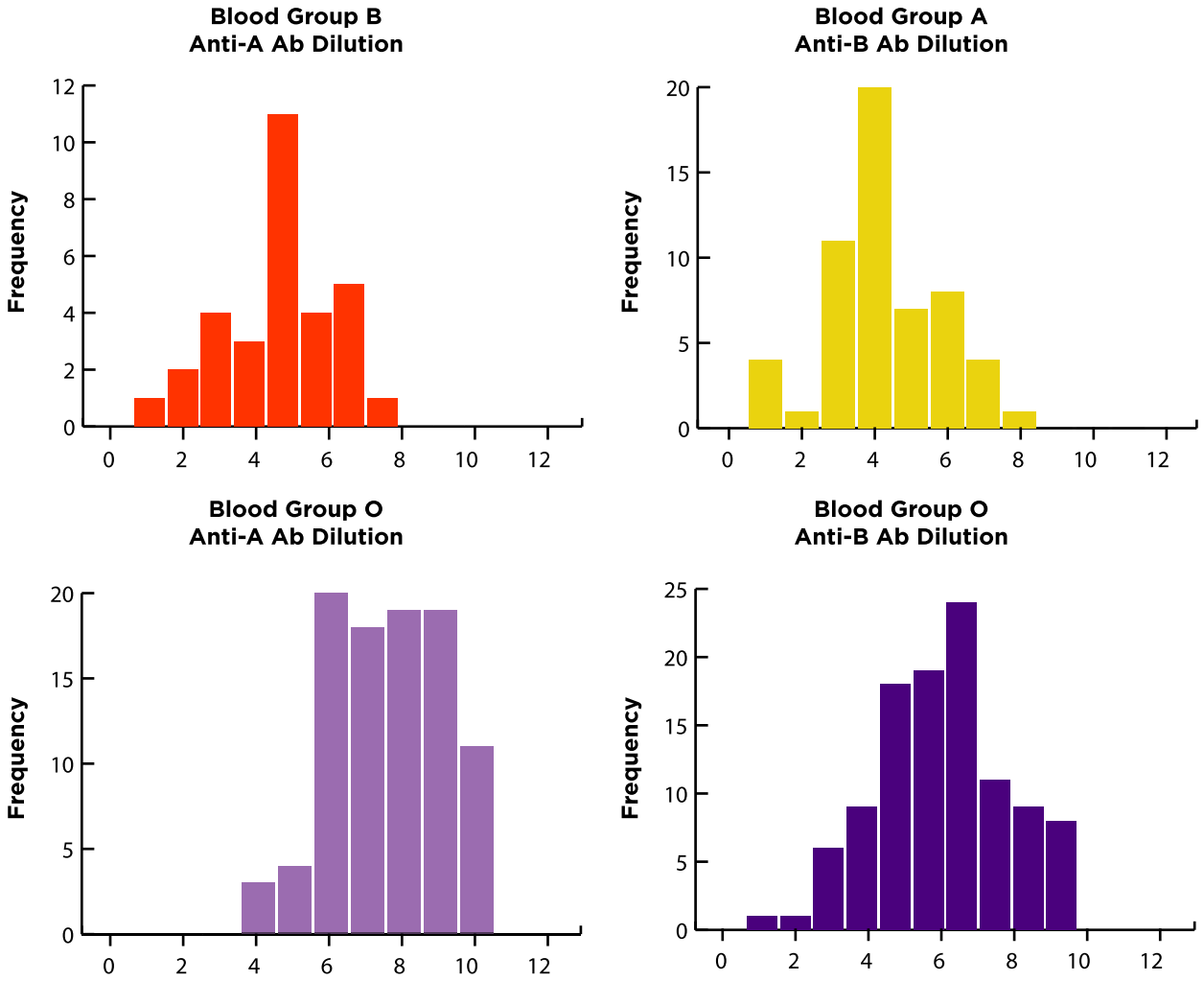

Figure 1 Distribution of anti A or Anti-B antibody titre (expressed as dilutions), by blood group.

antibody dilutions (Pearson correlation coefficient 0.006). Interestingly, overall, there was no correlation between either anti-A or anti-B antibody dilution and cRF (Pearson correlation coefficient anti-A 0.17; anti-B -0.02).

Changes to anti-A and anti-B antibody with time

A subset of 70 patients who remained untransplanted following the first sample testing underwent a further measurement of anti-A or anti-B measurement 6 months after the initial antibody measurement. The majority (38, 54%) were blood group O; 36% blood group A; 7% blood group B and 2 blood group AB. Three patients were excluded from further analysis because of atypical blood group antibodies or because they were blood group AB, resulting in 65 anti-B measurements and 42 anti-A measurements for further analysis. One third (25, 36%) of patients experienced no interval change in antibody levels over a 6-month period. Of the 65 anti-B antibody measurements, the majority (56, 86%,) remained within +/− 1 dilution difference between the initial and subsequent measurement, see Fig. 2a. Anti-A antibody measurements, show a similar trend. Figure 2b.

Simulated ABOi transplantation

The number of adults who would be eligible to receive a deceased donor ABOi kidney transplant within the simulation, on the basis of their 'LOW' anti-A or anti-B levels, is shown in Table 4. At the start of the model, 35.1% of listed Blood Group B recipients and 64.5% of Blood Group A recipients would be eligible, while for Blood Group O recipients the proportion was lower (7.9%).

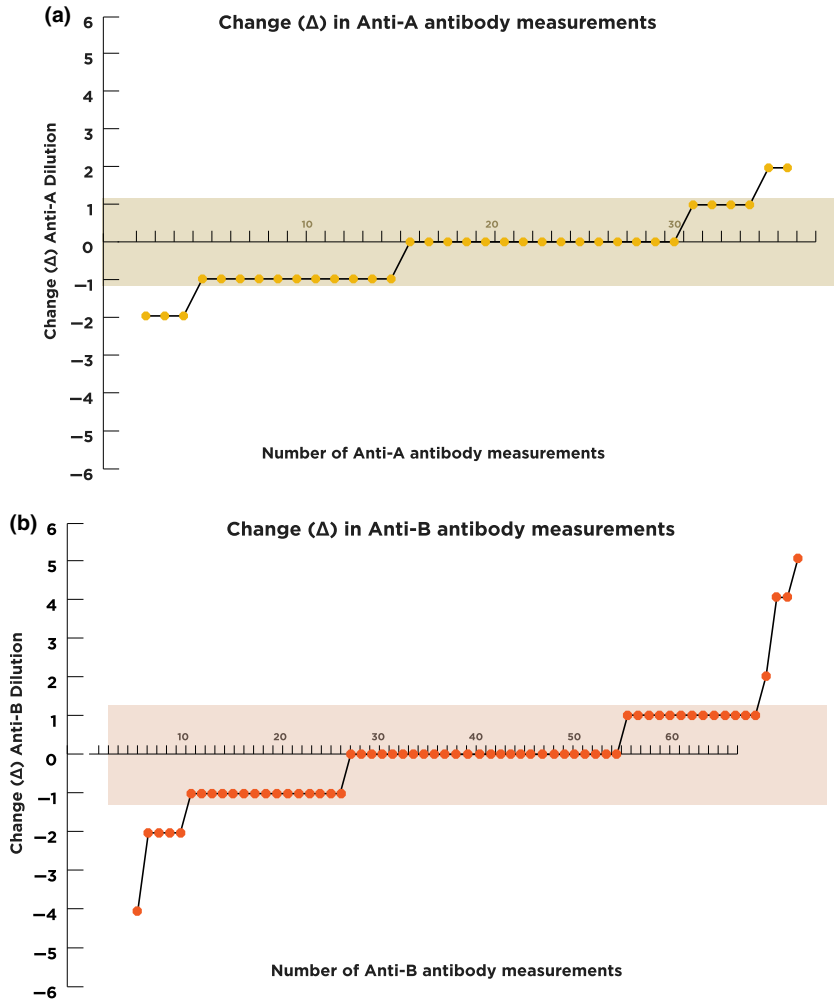

Figure 2 Demonstrating the difference (Δ dilution) in antibody dilution between (a) anti-A antibody levels taken 6 months after the initial sample, and (b) anti-B antibody levels.

Simulated transplant activity

Although total numbers of patients transplanted remained very similar in all models, permitting ddABOi allocation led to an increase in the numbers of 000 mismatched kidney allocations. Compared with 470 HLA Level 1 (000 mismatched) adult transplants achieved in the baseline simulation, SIM1 resulted in 508 HLA Level 1 transplants and SIM2 509 HLA Level 1 transplants. SIM4 resulted in the least number of HLA Level 1 allocations (469) and the greatest number of Level 3 allocations (852, compared with 841 in the baseline simulation). The overall detailed adult transplant activity over a period of 4 years, shown for each of the three simulations by allocation tier and HLA mismatch is available in Supplementary Table 2.

Simulated numbers of ddABOi

Using only recipients with Anti-A or Anti-B levels of ≤3 dilutions (≤1:8 titres), simulated numbers of intentional ddABOi are shown in Fig. 3 & Table 5. SIM1 resulted in 262 ABOi transplants, accounting for 13% of all adult kidney activity. SIM2 prevented blood group B donor kidneys being allocated to blood group A recipients, unless the HLA mismatch is 000 – this resulted in 212 ddABOi transplants. Interestingly, allowing Blood Group B kidneys to only be given to blood group B recipients - as in SIM3 – did not result in more blood group B recipients receiving a transplant. SIM3 resulted in 152 ABOi transplants in adults, 8% of all adult kidney transplant activity. Restricting ddABOi to only those who had waited for 7 years or more resulted in the fewest number (64) of adult ddABOi kidney transplants.

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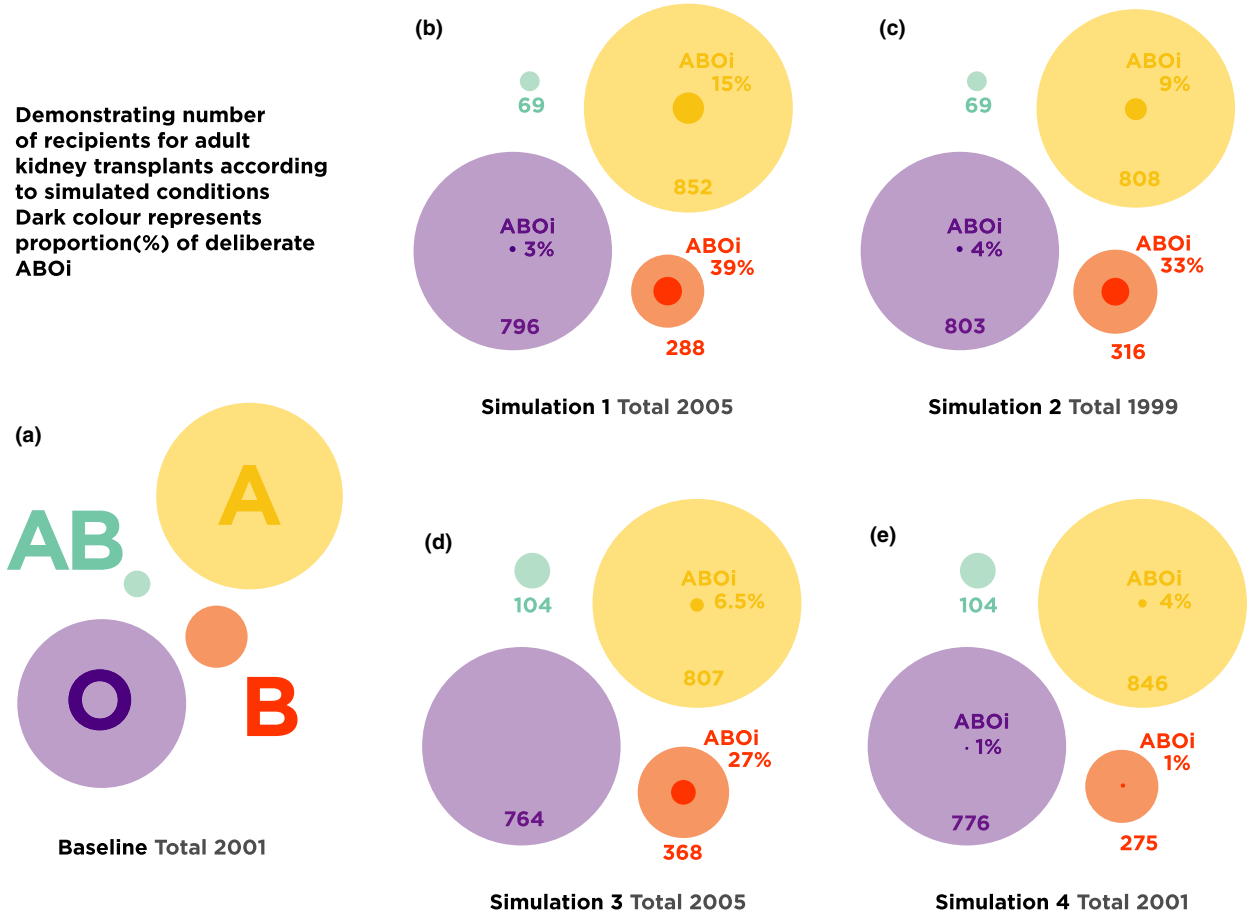

Figure 3 Demonstrating UK Adult allocation, by recipient blood group, demonstrating the proportional predicted numbers of deceased donor ABO-incompatible transplantation over a simulated 2 year period. Highlighted are the proportion (%) of deliberate ABOi transplants (a) the baseline model (b) SIM1 – permitting low antibody level ABOi allocation, (c) SIM2 – as for SIM1, but restricting blood group B donors to be allocated to blood group A recipients only if they are 000 HLA mismatch (d) SIM3 as for SIM1, but only permitting blood group B donors to be allocated to blood group B recipients. (e) SIM4, as for SIM1, but restricting low antibody level ABOi allocation to proceed for 'long-waiting' patients (listed for >7 years).

Simulated waiting time

Median waiting times for transplanted adults are shown in Table 6. Permitting ddABOi transplants resulted in an increased overall waiting time, particularly for Blood Group AB, but variation in waiting time across blood groups was reduced compared with the baseline.

Discussion

This study for the first time reports the distribution of ABO blood group system antibody distribution in the adult population awaiting a renal transplant, and demonstrates no correlation between high anti-A or anti-B antibody levels and anti-HLA antibody as measured by cRF. We have also simulated the effect if incorporating ddABOi allocation into the UK NKAS. Overall this would result in similar total numbers of adult kidney transplants, but permissive ddABOi would ensure that waiting times by blood group would become more equitable, in addition there was an unintended effect of an increased number of 000 HLA-mismatched organ allocations.

We demonstrate that there is no relationship between an increasing ABO-antibody titre and cRF, reflecting the biological distinction between antigen exposure and the development of antibodies incurred in ABO & HLA. ABO antibodies may be 'naturally' generated as a cross-reactive consequence to pathogen exposure within the gut [22], while development of anti-HLA antibody requires the prior inoculation of the immune system with the antigen as a result of prior transplantation, pregnancy or transfusion.

Table 4. Estimated proportions of adults on the transplant list expected to have low anti-A or anti-B antibody levels (≤1:8 titres or ≤3 dilutions or less) at the time of starting the simulation, and in patients added to the simulation as it progresses.

Transplant list Recipient blood group	**Low anti-A titres** (≤1:8 or ≤3 dilutions)		**Low anti-B titres** (≤1:8 or ≤3 dilutions)	
	N	%	*N*	%
O	0/3405	0	270/3405	7.9
A			1481/2296	64.5
B	339/966	35.1		
AB				
New patients added Recipient blood group	**Low anti-A titres** (≤1:8 or ≤3 dilutions)		**Low anti-B titres** (≤1:8 or ≤3 dilutions)	
	N	%	*N*	%
O	0/2132	0	174/2132	8.2
A			1149/1765	65.1
B	216/667	32.4		
AB				

As part of this simulation, we have highlighted that an unintended consequence of a change in allocation to permit ddABOi transplantation would be an increased number of 000 HLA mismatch transplants being undertaken overall. This is clearly a potential benefit to the transplant population at large. This unanticipated finding is in keeping with the way in which intentional ABOi transplantation is being used to achieve a more optimal HLA match within the paired scheme [23]. There is no head to head analyses comparing HLA-matching in ABOi transplantation to ABO-compatible transplantation. Ferrari *et al.* have, using simulations of the Australian national paired donor pool, demonstrated the positive effect of adding ABOi pairs to a Kidney Paired Donation (KPD) pool [24], as well as the potential effect of the KPD on improving HLA-matching of compatible pairs, however, a direct analysis of ABO-compatible with a poor HLA match, compared with ABOi with a favourable match is lacking. Nonetheless, for patients undergoing compatible transplantation, the benefits of 000 mismatch transplantation have been demonstrated to result in improved long-term graft outcomes, even in the context of increase in cold ischaemia times [25]. As a consequence, this by-product of the change in allocation, which results in up to a quarter of patients achieving a 000 mismatch allocation should be seen as a very positive outcome for a significant proportion of patients. In particular, it has been recently highlighted that optimal matching is highlighted by patients as being perceived to be the most important factor for kidney allocation in the UK [26].

Inherent in the simulation model are two significant assumptions. Firstly, that all eligible adult patients would be willing to accept an ABOi transplant. Secondly, that ABO titres remain stable over time. A limited number of the sampled patients underwent a second ABO titre measurement. Among those, the majority of titres remained stable – a third of patients' antibody measurements were unchanged, while a further 50% were within ±1 dilution of the original antibody measurement. This suggests that, for most patients, antibody levels are unlikely to fluctuate significantly over the duration of their time on the waiting list.

Clinically, there is a perception that low titre transplantation is immunologically 'safer' than high baseline titre transplantation, however, there is no demonstrable difference in long term graft outcomes or biopsy proven rejection when comparing 'high-baseline titre' patients (>1:256) to 'low-baseline titre' [2,27]. High anti-ABO titres at the time of transplantation (>1:32) have, however, been shown to be statistically significant as a factor in the risk of antibody mediated rejection [28]. The choice of 'LOW' ABOi patients in this model was therefore a pragmatic decision about patients for whom no treatment, or a single pretransplant antibody adsorption treatment, would allow timely deceased donor ABOi transplantation. If a higher antibody threshold were considered - for example anti-A or B antibody levels of <1:64, (<6 dilutions) - nearly all blood group A patients (98.2%) would meet the criteria, and over 50% of blood group O patients would similarly be eligible. In our experience, using double column immuno-adsorption (IA) has the potential to significantly reduce ABO antibody levels after a single treatment [29], however, it should be noted that there is demonstrable variation in ABO-antibody titre measurements between UK centres [30], which is why a more conservative 'LOW' threshold was used in this study.

The question of which of the simulation rules to choose is, in part, a question of risk perception regarding ABO incompatible transplantation, taken together with the overall improvements in equitable blood group allocation, and general benefits of greater rates of 000 mismatch allocation for the entire cohort. As authors, we are broadly in favour of SIM2 rules, in which Blood Group B kidneys are restricted to Blood Group A recipients, only if a 000 mismatch transplant is facilitated.

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Table 5. Demonstrating the anticipated simulated number of recipients, by blood group for adult kidney transplants, according to donor blood group. Highlighted transplants (% of recipient blood group) are deliberately ABO-incompatible. See Fig. 3.

	Recipient				
Donor	O	A	B	AB	Total
Baseline					
O	766	30	54	3	853
A		814		46	860
B			218	1	219
AB				69	69
Total	766 (38%)	844 (42%)	272 (14%)	119 (6%)	2001 (100%)
Sim (1)					
O	771	27	50	4	852
A		701	105 (36%)	57	863
B	25 (3%)	69 (8%)	125	1	220
AB		55 (7%)	8 (3%)	7	70
Total ABOi	25 (3%)	124 (15%)	113 (39%)		
Total	796 (40%)	852 (42%)	288 (14%)	69 (3%)	2005 (100%)
Sim (2)					
O	768	29	49	4	850
A		707	96 (30%)	58	861
B	35 (4%)	20 (2.5%)	162	1	218
AB		52 (6.5%)	9 (3%)	9	70
Total ABOi	35 (4%)	72 (9%)	105 (33%)		
Total	803 (44%)	808 (36%)	316 (17%)	72 (3%)	1999 (100%)
Sim (3)					
O	764	31	50	4	849
A		723	91 (25%)	52	866
B			219	1	220
AB		53 (6.5%)	8 (2%)	9	70
Total ABOi		53 (6.5%)	99 (27%)		
Total	764 (44%)	807 (36%)	368 (17%)	66 (3%)	2005 (100%)
Sim (4)					
O	769	27	53	3	852
A		787	22 (0.9%)	50	859
B	7 (1%)	14 (1.8%)	197	1	219
AB		18 (2.2%)	3 (0.1%)	50	71
Total ABOi	7 (1%)	32 (4%)	25 (1%)		
Total	776 (39%)	846 (42%)	275(14%)	104 (5%)	2001 (100%)

This allocation would result in around 10% of all kidney transplants being low titre ABO-incompatible, and lead to an improved equality of distribution of transplants across all four blood groups, as well as permitting 25% of the cohort over all to be allocated a 000 mismatch transplant. For those more conservatively minded, SIM4, which minimizes ABO incompatible allocation only to those patients who have been waiting for greater than 7 years, the overall numbers of patients receiving an ABO-incompatible are low (64 transplants), however, it should be noted that it results in no improvement in allocations to Blood Group B recipients (14%, the same proportion as in the baseline simulation), as well as fewer 000 mismatches.

There are of course potential barriers to implementation of this allocation scheme. Access to reliable out of hours ABO-antibody measurements is one concern, particularly in the light of evidence suggesting the variability in titre measurements with different techniques [30,31]. Another is the perceived increased immunological risk of ABOi transplantation. Montgomery *et al.* have clearly shown that over the medium and longer term, living donor ABOi transplantation is comparable to ABO-compatible transplantation [32], yet take up in

Table 6. Median waiting time, by blood group, of transplanted adult recipients demonstrating differences between baseline allocation rules, and simulated conditions permitting ABOi allocation.

	Baseline simulation	Simulation 1	Simulation 2	Simulation 3	Simulation 4
Blood group O					
Patients transplanted	766	796	878	764	776
Median waiting time (days)	2104	2043	1997	2110	2102
Q1–Q3	1306–2808	1269–2790	1246–2691	1330–2818	1303–2820
Blood group A					
Patients transplanted	844	852	724	807	846
Median waiting time (days)	1458	1488	1609	1540	1537
Q1–Q3	908–2132	895–2210	923–2365	922–2240	927–2206
Blood group B					
Patients transplanted	272	288	345	368	275
Median waiting time (days)	2009	1965	1778	1752	2056
Q1–Q3	1192–2882	1071–2832	1183–2584	994–2480	1225–2857
Blood group AB					
Patients transplanted	119	69	56	66	104
Median waiting time (days)	1104	1414	1584	1512	1183
Q1–Q3	637–1647	844–2031	890–2788	844–2208	777–1800
All adults					
Patients transplanted	2001	2005	2003	2005	2001
Median waiting time (days)	1742	1787	1804	1789	1793
Q1–Q3	1027–2558	1049–2589	1097–2578	1058–2584	1066–2598

the USA is low, partly related to concerns suggesting that there is an increased risk of graft loss in the first 14 days post-transplant [33]. Aggressive AMR following ABOi transplantation is not well-described or reported, although it may be part of the explanation for the risk of early (<14 days post-transplant) loss described by Montgomery *et al.* A possible reason for this may be that it has previously been suggested that ABO-titre rise post-transplant predicts risk of acute AMR [34]. Interestingly, amongst centres utilizing ABO-incompatible transplantation frequently, there is evidence that baseline ABO-antibody titre is not fully reflective of the risk of adverse outcomes in the short or long-term between patients with and without an ABO-antibody rise post-transplant [35–37]. In part, an explanation for this finding may relate to ABO-antibody readings not reflecting T-cell memory responses, which may be more influential in predicting ABOi recipients likely to reject.

In this study, we have made no distinction for A2 compared with A1. The immunogenicity of ABO antigen may not be equal, particularly given the considerable polymorphism in ABO subtypes [38]. The use of A2 to O or B recipients has been permissible and recommended for some time, resulting in a reduction in waiting times and comparable graft outcomes to conventional compatible transplantation [7,39]. Initially, the number of participating centres participating was low [40], however, the new Kidney Allocation Scheme in the USA has led to a significant increase in A2 donors being used for ABO-incompatible transplants [11]. Additionally, there is mounting evidence that for patients with low-titres of anti-A or anti-B antibody (<1:16), there is no requirement for any augmentation to conventional immunosuppression, or need for desensitization therapy with plasmapheresis [41–43].

For clinicians, this study challenges the conventional approaches to ABOi kidney transplantation, and suggests that adoption of low titre ddABOi has the potential not only to improve the equity of transplant waiting times across blood groups, but also contribute to improved HLA matching for the kidney transplant population as a whole.

Declarations

An investigator initiated grant was awarded by Glycorex to support antibody testing. Glycorex was not involved in any aspects of trial design, analysis or manuscript preparation.

Authorship

MM: designed & conducted the study, performed statistical analysis and wrote the paper. LB: analysed the data and

performed statistical modelling. NRB: assisted in study design, DOB, BS, DV & OS: performed the study. OS, NK & AD: contributed to study design and assisted with writing of the paper. SS: performed the study. NM: contributed to study design, analysis and drafting of the paper.

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Conflict of Interest

The authors report no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Changes to UK kidney allocation by blood group under the following rules: (a) Simulation 1 (SIM1) rules – deceased donor ABOi transplantation permitted for patients with low (≤3 dilutions or ≤1:8 titres) anti-A or anti-B levels (b) Simulation 2 (SIM2) rules, as for SIM1, but prevents blood group B donor kidneys being allocated to blood group A recipients unless the match is a zero HLA mismatch and (c) Simulation 3 (SIM3) rules prevent blood group B kidneys being allocated to either blood group A or O recipients. Simulation 4 (SIM4) rules are as for SIM1, but only allowing the incompatible transplant for long waiting (>= 7 years) adults.

Table S2. UK Kidney transplant allocation at baseline and under simulated conditions (SIM1, SIM2, SIM3, SIM4) permitting deceased donor ABO-incompatible transplantation demonstrating the numbers of simulated transplants and their UK Allocation Tier and HLA matching [21].

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