UK NEQAS
International Quality Expertise

Histocompatibility & Immunogenetics

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Interpretive Educational Scheme (iED)
Clinical Scenario 1/2018 – Renal Transplantation

Dispatched on 13th March 2018

Summary of Results

A total of 53 responses were received, 22 from UK & Ireland (UK&I), 31 from Rest of the World (RoW).

1. **Given the information above, would you recommend removing any HLA antibody specificities from the patient's unacceptable antigen profile to increase the chance of a deceased donor transplant offer?**

Decision	UK&I		RoW		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Yes	22/22	100%	28/31	90%	50/53	94%
No	0/22	0%	3/31	10%	3/53	6%

Reasons for answer:

Yes	Given the defined unacceptable antigens the patient is unlikely to receive a transplant within the 12-18 months before anticipated loss of vascular access. Lowering her CRF will greatly increase her chances of being offered a deceased donor transplant.
	Selected antibodies are likely transfusion-derived and potentially less pathogenic.
	There are clear temporal changes in the patient's antibody profile, e.g. historic positive current negative.
	Many specificities have reduced and now ~1000 or <1000, if all these removed would reduce cRF from 99% to 91%.
	Consider using higher threshold for UAG listing >3000 current MFI in this case to further increase chance of offer.
	Local guidelines are that unacceptable antigens are those with MFI>2000 and that UMM can be delisted if MFI<2000 for at least six months and measured on at least two occasions. Except DR15 and DR16 (excluded by DR51). B12 would remain as it is pregnancy derived and has not been MFI<2000 for long enough. New cRF 91%.
	We would aim to delist from only 1 loci at a time in the hope of obtaining only 1 mismatch against delisted antigens.
	We would discuss this patient at MDT to determine if medically fit to receive enhanced immunosuppression and then consider delisting specificities to improve chances of offers. Initially we would consider delisting specificities which are consistently <2000 MFI in the most recent (2+) samples. The exceptions are B44 which is pregnancy induced.
	Risk vs. Benefit: Clinical situation described needs a modified attitude to risk avoidance with regards to antibodies which has to be balanced against clinical risk to patient arising out of her access problem. Risks can be taken as long as known and manageable.
	Specificities currently below 1000 MFI can be removed, whilst those between 1000-3000 MFI should be reviewed and may be removed if this could improve her chances of transplant.
	Reduced reactivity for multiple specificities in current sample, may represent a window of opportunity for transplant.
	Any MFI specificity under 3,000 would be considered for removal. As equates to a negative FCXM (retrospective audit data).
	Not a standard practice to remove HLA antibody specificities, but after discussion with the Transplant team, some specificities may be removed due to: high cRF, losing vascular access and slim transplant chances as predicted by the ODT tool.

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	This labs cut-off for antibody detection is 1,500 MFI & for registering UAM's, the cut-off is 3,000 MFI. Specificities less than 3,000 are unlikely to cause a positive XM and can therefore, be removed. Specificites that have been neg for at least 1 year may also be removed. Some antibodies are likely to be transient following blood transfusions.
	Delete Antibodies with MFI under 2000 on the last sample (2018) and under 3000 on historical sample (2017-2016). Help this decision by perform an assay on denatured antigen (only class I antibody) and ability to bind the complement (like C1qscreen assay).
	There are a number of antibodies with low MFI (<4000) and no cross reactivity with possible immunizing pregnancy antigens. We would only remove these specificities when negative in CDC screening. B44 specificity not removed although MFI < 4000, because it is a pregnancy antigen.
	The following antigens remain unacceptable: repeat mismatches with the partner and antibodies that are detectable against these antigens. Current/historical MFI >5000; current MFI >3000; important CREG B44-45.
	Only plausible antibodies, i.e. antibodies induced by pregnancies and antibody specifities with MFI >10000 are considered as unacceptable.
	The patient has cRF of 99% so this rate should be reduced by applying plasmapheresis.
	We would increase cut-off for unacceptable antigens to MFI<3000. In his scenario we would demand a prospectively negative CDC crossmatch both B cells and T cells. We would also add Rituximab and IVIG to the immunsuppressive treatment. We would consider to increase cut-off for unacceptable antigen to MFI<5000 and provide PE in relation to surgery.
No	We recommend removing HLA antibody specificities with reactivities less than 2000 MFI for more than 3 years and excluding specificities reacting against eplets shared by her partner's HLA. No specificities match to this rule. In our policy antibodies after transfusion must be checked at 14D, 1M, 3M. We should check isolated anti-DR8 specificity.
	All unacceptable antigens are mean of fluorescense intensity (MFI) superior to 1000 in last year.

If yes, please detail the specificities that you would recommend for removal with reasons:

HLA Spec	Number of labs agreeing to remove Spec (out of 50)			Reason(s) for removal from unacceptable antigen profile
	Total	UK&I	RoW	
A1	41	20	21	Low MFI anticipate current CDCXM/FCXM negative
				Low MFI, same CREG as patients own A3. Makes acceptable the common A1 B8 DR17 haplotype
				current ~ / <1000MFI our UAG listing cut-off
				MFI<2000 for >6 months
				Not partner MM
				Most recent samples MFI below or around 1000 MFI
				current at ~1000 MFI, peak ~2700
				Under <3000 MFI
				current MFI <2000, Peak MFI <3000. Common antigen.
				Always under 5000 MFI
				No shared epitope with HLA antigens responsible for sensitization
				Virtual Crossmatch neg, A1 often detected as 'denatured'Ag
				MFI < 4000
				no plausible immunisation to a previous transplant or pregnancy; MFI<10000
A2	1	0	1	Strong crossreactivity A69,Crossreactivity A23,A24
A23	39	19	20	Anticipate current CDCXM/FCXM negative
				current <1000 MFI our UAG listing cut-off, previously weak
				MFI<2000 for >6 months
				Most recent samples below 1000 MFI

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				May be pos due to crossreactivity with 70KA epitope
				Always under 5000 MFI
				Not pregnancy-related mismatch
				virtual Crossmatch neg
				MFI < 4000
				MFI <3000
A24	37	19	18	Low MFI, anticipate current CDCXM/FCXM negative
				current ~ / <1000MFI our UAG listing cut-off. previously weak
				MFI<2000 for >6 months
				Under <3000 MFI
				May be pos due to crossreactivity with 70KA epitope
				Always under 5000 MFI
				no plausible immunisation to a previous transplant or pregnancy; MFI<10000
				MFI < 4000
A69	36	17	19	anticipate current CDCXM/FCXM negative
				Decreasing MFI, same CREG as patients A68
				current <1000MFI
				MFI<2000 for >6 months
				Historic Pos; Current Neg
				not pregnancy-related or transplant related mismatch
				virtual Crossmatch neg
				MFI titer is less than 3000
				MFI < 4000
B27	6	1	5	current MFI <2000
				MFI <3000 ON LAST SERUM
				Low and stable MFI value
B37	7	1	6	current MFI <2000, Peak MFI <2000
				MFI <3000
				MFI <1000, not part of creg
B38	5	1	4	current negative, Peak MFI <2000
				always below 3000 and decreasing MFI
B39	7	1	6	current MFI <2000, Peak MFI <2000
				MFI <3000 ON LAST SERUM
				Strong crossreactivity B38
B42	4	2	2	Review after agreed time period - remove all under 6000 MFI
				Always under 5000 MFI
				no plausible immunisation to a previous transplant or pregnancy; MFI<10000
B44	10	4	6	current <2000 MFI with note of caution if MM - due to known previous route of sensitisation
				Under <3000 MFI
				Currently below cut off, would monitor and crossmatch any donor with this mm due to pregnancy
				potential immunizing antigen but still low reactivity
				Strong crossreactivity B45
B45	16	8	8	anticipate current CDCXM/FCXM negative
				current <2000MFI with note of caution if MM - due to known previous route of sensitisation
				MFI <2000 in 2/4 sample dates, including 2 most recent
				Under <3000 MFI

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				not pregnancy-related mismatch
				low MFI, virtual Crossmatch neg
				MFI<5000
B49	2	0	2	no plausible immunisation to a previous transplant or pregnancy; MFI<10000
				Strong crossreactivity B50
B50	1	0	1	no plausible immunisation to a previous transplant or pregnancy; MFI<10000
B56	5	2	3	Always under 5000 MFI
				no shared epitope with HLA antigens responsible for sensitization
				no plausible immunisation to a previous transplant or pregnancy; MFI<10000
B58	1	0	1	Crossreactivity B59
B59	6	1	5	current MFI <2000
				MFI <3000 ON LAST SERUM
B13	27	16	11	anticipate current CDCXM/FCXM negative
				MFI<2000 for >6 months
				Under <3000 MFI
				current MFI <2000, Peak MFI <5000. Common antigen
				not pregnancy-related mismatch
				Crossreactivity B37
B62	1	0	1	Strong crossreactivity B76,B63, Crossreactivity B57,B75
B63	22	14	8	anticipate current CDCXM/FCXM negative
				MFI<2000 for >6 months
				Under <3000 MFI
				Always under 5000 MFI
				no plausible immunisation to a previous transplant or pregnancy; MFI<10000
B67	5	2	3	Review after agreed time period - remove all under 6000 MFI
				no plausible immunisation to a previous transplant or pregnancy; MFI<10000
				Crossreactivity B39, B56
				MFI<5000
B71	3	1	2	Always under 5000 MFI
				no plausible immunisation to a previous transplant or pregnancy; MFI<10000
				Strong crossreactivity B72
B72	1	0	1	no plausible immunisation to a previous transplant or pregnancy; MFI<10000
B75	27	18	9	anticipate current CDCXM/FCXM negative
				Decreasing MFI, low MFI in current sample, Negative in 02/2017
				MFI<2000 for >6 months
				current MFI <2000, Peak MFI <5000
				MFI titer is less than 3000
				no plausible immunisation to a previous transplant or pregnancy; MFI<10000
				MFI always <5000
B77	27	15	12	anticipate current CDCXM/FCXM negative
				MFI<2000 for >6 months
				Historic positive, current negative, Peak MFI <5000
				no plausible immunisation to a previous transplant or pregnancy

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B55	14	4	10	current <3000 MF
				Review after agreed time period - remove all under 6000 MFI
				no shared epitope with HLA antigens responsible for sensitization
				low MFI, virtual Crossmatch neg
				Strong crossreactivity B56, Crossreactivity B42
				MFI<5000
Cw5	1	0	1	too high MFI value
DR7	12	4	8	current <3000MFI with note of caution if MM - due to previous route of sensitisation
				Review after agreed time period - remove all under 6000 MFI
				Always under 5000 MFI
				MFI <3000 ON LAST SERUM
				no plausible immunisation to a previous transplant or pregnancy; MFI<10000
DR8	30	16	14	Review after agreed time period - remove all under 6000 MFI
				anticipate current CDCXM/FCXM negative
				potentially transfusion-derived
				Only seen once - doesn't fit with historical profile, current neg
				positivity inconsistence and no share Ep with DR1
				Antibody did not appear in subsequent testing. ? false positive
DR9	7	2	5	Review after agreed time period - remove all under 6000 MFI
				MFI always <5000
				no plausible immunisation to a previous transplant or pregnancy; MFI<10000
				Strong crossreactivity DR7
DR1	1	0	1	Strong crossreactivity 103,DR10,DR15,DR16
DR10	13	5	18	current 3 screens <3000 MFI
				Always under 5000 MFI
				no plausible immunisation to a previous transplant or pregnancy; MFI<10000
DR15	33	14	19	Single antigen bead MFI <2000 MFI in the last 12 months
				MFI <2000 in all sample dates - would not increase chances due to listing of DR51
				Always under 5000 MFI, it is unclear why these specificities were EVER listed as have never even been >1000 MFI
				Specificities are below 2000MFI in the most recent sample and not pregnancy-related mismatch
				Low MFI
DR16	34	15	19	anticipate current CDCXM/FCXM negative; potentially transfusion-derived
				MFI <2000 in all sample dates - would not increase chances due to listing of DR51
				Always under 5000 MFI, it is unclear why these specificities were EVER listed as have never even been >1000 MFI
				Low and stable MFI value
				MFI<1000
DR51	9	4	5	Potentially transfusion-derived; proceed with caution
				Review after agreed time period - remove all under 6000 MFI
				Not removing negates removal of DR15,16
				we do not exclude from final XM based only to broad specificity

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2. Would you perform any additional testing, or make any additional recommendations to help increase the chance of the patient receiving a deceased donor transplant?

Decision	UK&I		RoW		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Yes	20/22	91%	28/31	90%	48/53	91
No	2/22	9%	3/31	10%	5/53	9

If Yes, please give detail:

Test serum samples with another method (e.g. Lifecodes).
EDTA treat samples or perform dilution studies to assess any prozone effect.
Test samples with the C1q assay to determine if her unacceptables are complement fixing.
Third-party crossmatching to de-listed specificities e.g. DR15 and DR16.
Consider live donors, including: NLDKSS, ABi and ABOi.
Clarify antibody class and IgG isotype.
Additional patient genotyping for DPB1 and DQA1.
High resolution (eplet studies).
Check anti-A and anti-B titres for ABOi Tx consideration.
Recommend exploring antibody reduction therapy or put forward for ITOPS trial.
If no offers received, remove HLA specificities < 5000.
Retest 02/2017 to check DR8 result.
Review local DCD/Fast track offers - prioritised allocation.
Allow repeat mismatch of partner where no sensitisation (DQ5).
HLA-selected blood transfusions.
Suggest plasma exchange/ plasmapheresis to try and reduce HLA antibody levels and regular post-exchange HLA antibody specificity monitoring to review HLA antibody MFI levels.
After removing the specificities listed above, the predictive tool could be repeated to see what difference this makes to the likelihood of this patient receiving a deceased donor tx. If necessary, de-listing specificities with reactivity > 3,000 could also be considered and with consultation with the clinical team.
Recommend patient counselling for consent to higher risk.
ICDC panel screening + HLA typing of the two children.
Perform donor's and recipient's high resolution HLA-analysis to compare the Luminex high resolution results and to use HLA-matchmaker.
Perform an auto-cross match (likely negative) to avoid confusing allo cross-match interpretation.
Determine acceptable mismatches and submit in AM program.
Transplantation possible in the presence of DSA (LX-MFI <10000) with immun-adsorption before and after transplantation (increased immune suppression).
Accept one DSA with MFI between 2000-5000 or several DSA with a cumulative MFI < 5000.

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3. Based on the results of the live donor testing, what would you recommend and why?

Discontinue transplant work-up: A2*, B44 and Cw5* are pregnancy-derived unacceptables (robust anamnestic response) (* also, high MFI 01/2018); CDCXM/FCXM positive and high LCS suggests sufficient antibody removal may not be feasible pre-transplant. Also, ABOi. Note potential donor APKD requires investigation.
Not to use this donor as it is a high risk transplant. The donor is ABO and HLA incompatible due to high MFI DSA. This would also be a transplant veto due to CDC and Flow crossmatch positive results, giving a high risk of hyperacute rejection.
Do not proceed with tx - strong FC and CDC XM pos =high risk of HAR - contraindication Class I DSA A2=13071, B44=1474, Cw5=18465, cumm=33,010MFI, not suitable for desensitisation.
We would recommend entering the pair onto the paired/pooled sharing scheme to obtain an ABO and HLA compatible donor.
Consider entering UKLKSS. If still unsuccessful, consider (HLA / ABO) antibody reduction therapy.
Contraindication to transplant according to BTS/BSHI guidelines. Donor is ABO incompatible. Luminex cumulative DSA = MFI 33,010 (HLA-Class I, pregnancy induced). CDCXM +ve with DTT, T&B cell FCXM strong positive indicating presence of complement fixing IgG HLA antibodies. Recommend entering patient and niece in paired/pooled kidney exchange.
Not to go ahead with this donor - positive flow and CDC makes it high risk. The recipient has DSA against A2 (MFI ~13000) and Cw5 (MFI ~18500). The donor is ABO incompatible with the recipient, the recipient may have anti-A antibodies which could cause hyperacute rejection. We would recommend entering them into the paired/pooled sharing scheme.
Discuss in MDT/Desensitisation meeting with clinical team, perform auto crossmatches to investigate the strength of allo-crossmatch reactivity and test for ABO anti-A titres to assess risk. Consider paired kidney sharing scheme to minimise immunological risk. ABOi + HLAi transplant would be last option.
Entering paired scheme. CDC and Flow XM positive, multiple DSA, repeat pregnancy haplotype mismatch with antibody - all indicators of poor prognosis for direct transplant.
The transplantation with the patient's niece as a live donor is contraindicated because of positive CDC and flow cytometry cross matches. Moreover there are 3 DSA (Anti A2, B44 and Cw5; cumulative MFI on current serum: 33010)
Avoid transplanting with her niece because presence of DSA against HLA-A2, B44, Cw5. Furthermore, these antigens are shared with patient's partner.
Blood group incompatible, A2 and Cw5 MFI > 4000 and positive crossmatches are all a contra-indication. A2, B44 and Cw5 are pregnancy antigens.
I would consider this an unacceptable high risk donation recommend domino/kidney sharing scheme (unlikely to respond to desensitisation).
No transplantation with patient's niece because the two XM (by CDC and FC) are positives (Anti-A2 and Anti-B44). Moreover, the patient's niece have certain antigens identical with HLA antigen of the patient's children father (A2, B44, Cw5, DR13, DQ7). Plus transplantation in a context of ABO incompatible.
With two unacceptable antigens among the niece's HLA profile and positive CDC XM and FCXM (IgG positive), allograft is not recommended. The CDC XM and FCXM positive results could be partly due to anti A2 antibodies corresponding to her husband's homozygous HLA-A2 profile.

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4. What unacceptable antigen profile would you use when registering the pair in the kidney-sharing scheme?

		UK&I (n=22)		RoW (n=31)		**Total (n=53)**	**Percentage**
		Number	Percentage	Number	Percentage		
Option 1	**Same profile as original deceased donor profile**	0	0%	4	13%	**4**	**8%**
Option 2	**Modified deceased donor profile (answer to Q2)**	16	73%	20	65%	**36**	**68%**
Option 3	**Other**	6	27%	7	22%	**13**	**24%**

Reason for answer:

Option 1	We do not participate in such a paired/pooled kidney sharing scheme. Nevertheless option 1 seems better in our opinion.
	Our non-active desensitization protocol (question2) is only available for deceased donor transplant.
	This represents a risk to donor as well as recipient.

Option 2	If the profile was kept the same as the original deceased donor profile the patient would have minimal chances of receiving a match through the paired/pooled scheme. Listing a modified deceased donor profile would increase the chances of getting a matched exchange.
	Maintain a relatively conservative approach (as per table in question 2), in the first instance with the option of modifying the acceptance criteria further if unsuccessful after 1 or 2 matching runs.
	Lower CRF gives a higher chance of being matched with a HLA compatible donor. If the donor is HLAi by only delisting a few antigens means that it is unlikely to result in a time of transplant positive flow crossmatch.
	We would recommend delisting based on our deceased donor profile (<2000 in 2+ recent samples, except pregancy induced specs). If no matches are generated in the initial run we would discuss at MDT and consider delisting all specificities consistently <5000 in most recent samples and enter into next run.
	Reducing her cRF will increase her chances of getting a match in the paired/pooled run, but runs the risk that a matched donor may have multiple mismatches corresponding to the removed specificities. If more time was available a couple of runs could be performed with her original profile, and then specificities removed if no matches are found.
	likely that the opinion of the living donor MDT would be that, at least initially, to keep the unacceptables listed the same as for the deceased list. Most of the other specificities have had historic levels in sample from 10/2016 at >3000 MFI, which would likely give a historic FC-XM pos, an observed risk in our local HLAi cohort for AMR.
	That would be the locally agreed policy to register only HLA antibody specificities >3,000
	Increase this patient's chance of receiving a decease donor transplant sooner. Based on the limited period left for vascular access, this patient has up to 3 opportunities to be entered into the KSS.
	I would initially put the patient in with the modified antibody profile from question 2, if

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	unsuccessful in number of cycles agreed with clinical team (usually three but may be reduced in this instance due to impending loss of dialysis access) then additional risk could be taken with the further removal of HLA-B41,49,50,72, and DR8 from profile .
	A less strict profile will give better chances for finding a donor.
	not the option 1 because of no more change than with cadaveric donor, not the option 3 because of the high risk of rejection.
	Provide an intermediate risk for the transplantation. Associate a specific pre and post transplantation treatment for desensitization = extra corporeal Ab removal therapy if MFI > 5000 or positive flow XM on current sera. Increase the immunosuppressive drugs after transplantation.

Option 3	**Reason**	**If 'other', detail specificities for unacceptable antigens**
	As clinically urgent, consider increasing threshold for listing UAGs further to increase chance on P/P ie >6000MFI. If successful pending on any donor DSA/levels and XM results - use augmented IS as appropriate with or without desensitisation protocol to remove/lower any DSA to acceptable levels (<2000) prior to transplant.	All >6000MFI due to clinical urgency. Routinely >2000- 3000 and is case dependent. A2, B62, B57, B58, B49, B72, Cw5, DR1, DR103 UAGs removed with known route of sensitisation to be considered with caution
	Removing all HLA specificities < 5000 will improve her cRF to 81 and improve her chances for a donor offers	All HLA specificities < 5000
	The cumulative DSA MFI would be assessed at the time of entering into the pool. Antibody specificities would be removed as unacceptable stepwise in accordance with policy.	Would remove specificities in a stepwise manner. If no offer in pool would reassess with policy to remove specificities.
	Starting with a conservative to liberal approach (including listing as 222 match grade). Can crossmatch and use desensitisation techniques as with other live donation. Providing offer is of no higher risk than available LRD - can proceed as HLAi.	All antibodies above 6000 MFI - not likely to result in CDC reactivity (ensure multiple 'hits' are avoided).
	A few cycles with same profile and then possibly remove specificities from unacceptables as discussed with transplant team. Encourage unit to send more frequent samples. Carry on with cellular work to identify negative-crossmatch antibodies. Avoid removing many specificities to minimise chance of getting a positive crossmatch.	HLA-A2, B62, B76, B57, B58, B49, B50, B41, B42, B56, B67, B71, B72, Cw5, DR1, DR9, DR103, DR51
	Deceased donor profile to question 2 but I delete also antibodies positive for denatured antigen.	I don't know the result of denatured assay
	Even with the modified deceased donor profile, cRF is still very high and the probability of finding a compatible donor are very low. With living donation, we would have more time to perform crossmatches and then decide according to the results obtained.	A2, A69, B57, B58, B62, B76, B13, B75, B77, B71, B72, Cw5, B44, B45, B41, B50, B49, DR1, DR103, DR9, DR10, DR15, DR16, DR51
	Due to medical emergency and taking into account that is living Tx (no cold ischemia time) we would accept all specificities in current sera MFI<3000, expected to give negative XM.	in addition to modified donor profile: B44
	When the current and historical MFI are <2000, these antigens will not be considered as unacceptable if the CDC and flow crossmatch are negative unless it concerns	All the unacceptable antigens as proposed except for A1, A23, A24, A69.

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	antigens of the partner against which antibodies were detected. Our criteria for LRD are more stringent than for a deceased donor (no option 1).	
	Table modified with remove of DR8, A24. Add DR13 as partner HLA: risk increased.	+DR13 -A24 -DR8
	Specificities with MFI>2000 in the most recent serum are added to the unacceptable antigen profile	A2, B44, B62, B57, B58, B41, Cw5, DR1, DR103, B76, B49, B50, B42, B55, B67, B71, B72, DR7, DR9, DR10, DR51.
	No comment	All antibodies with MFI > to 1000 are unacceptable antigens. So we will add the B38, B39, B27, B37 and B59 as unacceptable antigens and remove DR8 in function of reanalyse.

5. Before any testing is performed, you are asked to provide the patients clinician with a predicted crossmatch result. What CDC and/or flow cytometry crossmatch result would you predict for the exchange donor and patient in your laboratory?

	Predicted Crossmatch Result								
	Positive			Negative			Other		
	UK&I	RoW	Total	UK&I	RoW	Total	UK&I	RoW	Total
CDC	0	0	**0**	22	30	**32**	0	0	**0**
Flow Cytometry	1	5	**6**	11	17	**28**	10	8	**18**

Reasons for Answer:

Some publications have attempted to correlate a MFI >2000 with a positive FCXM. 01/2018 donor-directed antibodies to A1 (1105) and A24 (1062) have a cumulative MFI 2167. Predicted FCXM outcome: Undetermined.
There is a low cumulative DSA MFI of 2867 and this would not be expected to give a positive CDC or flow cytometry crossmatch result.
DSAs A1= 1105, A24=1062 too weak to cause complement activation and pos CDC. Current cumm DSA ~2167 FCXM negative/weak pos, historic >4000 - likely pos (weak)
MFI of DSA are not high enough to elicit cytotoxic response. May observe historic, equivocal B-cell positivity by flow cytometry.
We would expect the flow and CDC crossmatches to be negative, combined MFI < 5000, unlikely to give a positive flow crossmatch. But we would mention to clinicians that antibodies against HLA-A1 and A24 were removed from the patients profile in the work-up to the sharing scheme.
DSA MFI below 3000 shown to be FCXM neg and CDC neg (at our centre).
The patient has DSA against A1 and A24, cumulative MFI 2167, these have been higher in historic samples so the FCXM would be predicted to be current negative but historic positive. The CDC crossmatch would be negative despite the presence of DSA, due to the low MFI levels.
Difficult to predict the FC-XM result just based on these MFIs. We would recommend full wet XM in our report.
Negative as study has shown cumulative MFI <5,000 would result in negative FCXM in local centre
CDC negative due to low cumulative MFI HLA Class I donor specific antibodies. Flow cytometry crossmatch more

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sensitive technique, possible historic positive and current crossmatch negative due to weak HLA Class I donor directed antibody.
The combined MFI of the A1 and A24 would suggest a negative CDC crossmatch. We would anticipate the flow being close to the cut off therefore would class this as an other or weak pos prediction. Wet crossmatch recommended.

Sensitivity of our flow cytometry crossmatch (MFI betwee 2500-3000).
Sensitivity of our CDC crossmatch (MFI more than 4000 and able to bind complement).

The patient only has antibodies against HLA-A1 and A24 (2167 cumulative MFI); these antigens don't share any antibody-verified eplet with the sensitizing event (pregnancies, as blood transfusions don't increase the sensitized profile); if the assay is performed with EDTA treated sera we believe that the crossmatches would be negative;

Sum of DSA = 2167 (A1=1105 and A24=1062), negative CDCXM as DSA MFI <6000-8000, equivocal FCXM for a MFI around 2000.

It is more likely the XM results will be negative because both the HLA antigens profile is removed and there is 1B,1C,1DQ HLA compability with the potential donor.

6. What level of immunological risk would you assign to this transplant?

	UK&I (n=22)		RoW (n=30)		Total (n=52)	Percentage
	Number	Percentage	Number	Percentage		
Standard	1	4%	0	0%	**1**	**2%**
Low	3	14%	4	13%	**7**	**13%**
Intermediate	18	82%	20	67%	**38**	**73%**
High	0	0%	5	17%	**5**	**10%**
Contraindication	0	0%	1	3%	**1**	**2%**
Other	0	0%	0	0%	**0**	**0%**

Reasons for answer:

Standard	FCXM = T & B cell neg. CDC = T & B cell neg. DSA MFI = 2867. Standard risk according to BSHI Guidelines: Guidelines for the detection and characterisation of clinically relevant antibodies in allotransplantation.
Low	Current DSA negative - weak historic. Not known sensitisation event or due to pregnancy. CDC negative - current and historic. Could be low - intermediate but more than standard risk.
	Higher than standard risk due to low level DSA however given that CDC is historically negative and flow cytometry is currently negative and only weakly positive historically I would be comfortable to proceed with intermediate risk.
	The Flow Crossmatch is currently negative and the CDC Crossmatch has always been Negative and the cumulative DSA MFI has decreased since 2016.The patient can undergo heightened immunosuppression.
	CDC XM and FCXM last results are negative in 03/2018. CDC XM results have always been negative.
Intermediate	According to BTS/BSHI guidelines a negative CDCXM, positive historic FCXM, current negative in presence of low level IgG Class I DSA corresponds to an intermediate immunological risk of early antibody mediated rejection.
	The current MFI levels of DSA and crossmatch results indicated that the overall risk level of transplant is intermediate. The risk of hyperacute rejection is low, however risk of accelerated antibody mediated rejection due to memory response is higher due to historically positive Flow crossmatch.
	Circulating CI DSA <5000MFI (cumulative), Historic Positive FCXM. Negative CDC crossmatch

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	however. Increased risk of AMR, but transplant possible with augmented immunosuppression and increased post tx monitoring.
	Based on BSHI/BTS guidelines, crossmatch results and risk of anamnestic response, MFI values and poor HLA match grade.
	Not standard or a contraindication. Low to Intermediate risk due to possibility of a memory antibody response to non-pregnancy associated specificities. Appropriate clinical caution needed, e.g. consider enhanced immunosuppression, proactive use of clinical intervention strategies e.g. plasma exchange, and post-transplant antibody monitoring.
	We believe that a transplant with DSAs can never be assessed as low risk; the risk is still intermediate because HLA-A24 and A1 are DSAs consistent positive within luminex panels, with antibody-verified eplets; this is consistent with the historical crossmatch positive FCXM.
	The recent cumulative MFI is approximately 3000 with negative CDC and FCXM, whereas cumulative MFI with historical serum is approximately 4100 and the historical FCXM are positive.
High	No ABO incompatibility and CDC crossmatch negative. But Historical Flow cytometry crossmatch positive (2017) on T-cells. And 6 mismatches in rejection direction.
	DSA > 3000MFI and FCXM positive in T and B.
	Positive XM results with the previous serum samples (2/2017, 10/2016) predict for a memory responce against this antigens (A1, A24).
Contraindication	The recipient has preformed DSA.

7. What level of immunological risk would you assign to this transplant?

	UK&I (n=22)		RoW (n=30)		Total (n=52)	Percentage
	Number	Percentage	Number	Percentage		
Standard	0	0%	1	3%	**1**	**2%**
Low	0	0%	2	7%	**2**	**4%**
Intermediate	18	82%	16	53%	**34**	**65%**
High	2	9%	8	27%	**10**	**19%**
Contraindication	0	0%	1	3%	**1**	**2%**
Other	2	9%	2	7%	**4**	**8%**

Reasons for answer:

Standard	None given.
Low	Remote sera positive FCXM, but negative CDCXM.
	CDC Crossmatch Negative against all samples. Flow Crossmatch became Negative when the MFI of the DSA dropped below 3 000.
Intermediate	BSHI/BTS Guidelines categorise historic positive current negative T/B cell FCXM (CDCXM negative) due to current IgG class I DSA as intermediate risk. Note: The HLA-B44 donor mismatch is also a pregnancy immuniser.
	The risk of hyperacute rejection is low. However risk of accelerated antibody mediated rejection due to memory response is higher due to historically positive Flow crossmatch. There is also increased risk above the standard as the B44 DSA is due to a known sensitisation event, pregnancy.
	Circulating CI DSA <5000MFI (cumulative), Circulating B44 type against partner mismatch. Historic Positive FCXM. Negative CDC crossmatch, however, increased risk of AMR, but transplant possible with augmented immunosuppression and increased post tx monitoring.
	Based on the BSHI/BTS guideline this transplant is considered an intermediate risk. As the crossmatch is positive in the 08/2017 sample it would need careful discussion with the clinical

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	team. In view of the urgency for transplant we would still proceed and to consider enhanced immunosuppression with post-transplant ab monitoring if indicated.
	Only DSA with SAB with neg current XM but with possible reactivity against children HLA (B44). If historically B44 found with CDC it would be high but not contraindication.
	The recent cumulative MFI is approximately 3000 with negative CDC and FCXM, whereas cumulative MFI with historical serum is between 3000 and 6000 and the historical FCXM are positive.
High	Historically quite strongly positive (based on cut off values indicated). Higher risk than previous donor due to presence of repeat pregnancy mismatch. CDC negative throughout and current flow negative. Not a contraindication in a patient with distinct clinical need.
	No ABO incompatibility and CDC crossmatch negative and only three mismatches in rejection direction. But Historical Flow cytometry crossmatch positive (2017) on T-cells.
	In this case we are repeating and HLA-B44 from the previous sensitizing event, event that triggered the development of the highly sensitized antibody profile. Also, B44 has antibody-verified eplets that are shared with other antibodies (with higher MFI) also shared in the past (HLA-B41); this is consistent with the FCXM positivity.
	Positive XM results with the previous serum samples (8/2017, 2/2017, 10/2016) predict for a memory response against this antigens(-A1,-B44).
	-Historical FCXM is positive -Presence of 2 DSA anti-A1 and anti-B44. -B44 is a repeat MM with partner. -CDC XM is negative, so there is no formal VETO.
	High risk due to positive flow crossmatch on historical sera and historic, cumulative MFI of DSA >5000.
Contraindication	The patient has anti-B44 antibodies with high MFI on historic sera, directed against a antigen of patient's children father and the potential donor.
Other	Intermediate-High risk. Although intermidiate risk according to BSHI/BTS criteria, B44 is pregnancy induced antibody and recent data suggests that pregnancy antibodies respond earlier and more vigorously post transplant (Higgins et. al., 2015).
	Risk is very high. In our hands, flow cytometry crossmatch with 03/2018 serum sample would be also positive with T and B cells. Presence of DSA against HLA-B44 from immunization against partner. (Keep in mind that we do not participate in such a paired/pooled kidney sharing scheme).
	B44 remains a plausible unacceptable antigen, unless: 1) children do not possess B44 2) the antibody is proven to be allelespecific but not donor specific for scenario 1) and 2) the risk would be intermediate

8. What clinical advice would you offer for this transplant?

Whilst the BSHI/BTS guidelines suggest transplantation should be avoided if reasonably possible, the transplant is recommended given the anticipated loss of access in 12-18 months. Clinical caution and the proactive use of clinical intervention strategies is advised: e.g. enhanced immunosuppression, post-transplant antibody monitoring.
Proceed with carefully considered and augmented IS due to historic sensitisation/ immunological memory. Perform close post transplant monitoring with low threshold for intervention therapy.
On the basis that 2 donors were in the first cycle, it is likely that a better match (avoiding B44) could be achieved within 1-1.5yrs on the scheme (currently 4 cycles/yr). If this Tx were to proceed, consider pre-transplant Ab removal, induction with Campath & Rituximab. Close post-TxAb monitoring.
This transplant may be at risk of early rejection. Post transplant monitoring could be considered for 14 days, than as clinically indicated.
Transplantation may be undertaken with appropriate clinical caution. Consider for enhanced immunosuppression, proactive use of clinical intervention strategies and perform post-transplant antibody monitoring. Discuss clinical

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urgency with MDT and consider if there is time to re-enter patient into next matching run to find an alternative donor.
Risk adjusted management plan: Intraoperative campath, augmented e.g. triple immunosuppression (including MMF), plasma exchange pre and post-transplant, increased antibody monitoring post-transplant, low tolerance for intervention and biopsy.
The recipient has known DSA against A1 and B44, post transplant DSA monitoring at 1, 3, 6 and 12 monthly advised. B44 is a repeat pregnancy mismatch which may increase the risk. Her immunosuppression may need to be increased due to these risk factors.
Consider augmented immunosuppression, scheduled post transplant monitoring weekly for 1st month, then monthly for first 3 months, or as clinically indicated.
Increased immunosuppression, increased frequency of antibody monitoring post-transplant by SAg beads. Team should be ready to treat if needed and /or perform biopsy, if antibody increases post-tx testing by complement fixing assays may guide selection of treatment. Test immediately before transplant to determine MFIs of DSAs.
Increased risk of anamnestic secondary response due to repeat pregnancy mismatch (B44). Consideration for augmented immunosupression, clinical intervention strategies and post-transplant donor specific antibody monitoring including levels. Possible plasma exchange and antibody specificity monitoring immediately prior to transplant.
HLA-B44 is a pregnancy induced ab. Given that XM results are currently neg there is a chance that the memory B-cell response may be activated with this donor. However, given the time remaining for vascular access the unit need to consider this. No risk of hyperacute rejection & post tx monitoring is imp. Suggest proceeding with this tx as best option.
Published evidence tells us that pregnancy induced antibodies has a tendency to respond more vigorously after HLAi transplantation. Therefore in addition to augmented immunosuppression agreed with the clinical team, regular post-transplant antibody monitoring should also be performed
The clinical team is likely to accept kidney for this patient provided patient can tolerate enhanced immunosuppression. Due to the historic pos flow crossmatch results, the transplant is intermediate risk and recommend plasma exchange pre-transplant. The patient needs to be monitored closely for DSA post-transplant.
The patient should be aware of the risk of anamnestic antibody response to B44 and the likelihood of enhanced immunosuppression, including Rituximab. Proactive use of clinical intervention strategies, e.g. plasma exchange, may help reduce risk, and post transplant vigilance with antibody monitoring will help early detection of rejection.
Donor 2 because only 3 mismatches. Perform C1qscreen and denatured antigen before transplant Perform an high risk immunosuppressive treatment and follow antibodies by single antigen at least 1 week / 1-2-3-4 months after transplantation.
Due to medical emergency of the Tx, augmented immunosuppression may be considered and Tx is not contraindicated . Careful immunological monitoring post-TX.
The first donor proposed for exchange may be the only chance.
Reinforced immunosuppressive protocol must be used if the transplant would be done because of the presence of DSA on the day of the transplant.
Our advice is negative due to the high risk transplantation, but it is upon the clinicians to make the decision and consider adapted therapy.
Considering the patient's risk of death within the next 2 years and the low probability to find a deceased donor, I would advise to proceed this transplant
I would suggest the following: high specificity HLA DSA testing. If epitope specific DSAs, consider high risk reg mon ATG for pre-transplantation.
HLA-typing of the children is necessary for a recommendation. B44 remains as unacceptable antigen – contraindication B44 is no longer defined as unacceptable (not inherited) - intermediate risk
Antibody screening is recommended with in the FIRST MONTH. If no DSA is detected no further testing is needed during the first post transplant year. In case of detected DSA, a biopsy should be performed and it is positive for AMR. If the biopsy is negative another DSA tests should be performed with in first year.

General comments on the scenario

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This true-to-life problem solving exercise was an enjoyable process. The clinical scenarios served as a reminder that we must balance safe transplantation with facilitating the transplantation of challenging patients. It has been said that '90% of time should be spent on 10% patients'. It is important to consider the route of sensitisation.
Urgent need for transplantation may necessitate going ahead with a higher immunological risk to the transplant.
Special case with increased urgency to transplant and highly sensitised. Consider increased immunological risk and threshold for UAG listing for appropriate IS and desensitisation as necessary to increase chances of transplant vs risk of not being transplanted.
If the patient had received no offers (deceased or sharing scheme) the delisting process would be expanded to include HLA-B and C, generally with MFI < 2000. We would aim to keep CRF >85% to keep the patient categorised as highly sensitised and a long waiter for points allocation in the deceased donor algorithm.
We do not usually delist pregnancy-induced DSA and would not have received the paired pool offer. Our answers are on basis of all Luminex testing being performed using EDTA treated sera as this is our standard protocol. Some labs may also consider comparing Lifecode/Labscreen Luminex results when considering delisting, however we only use one.
Before removal of unacceptable specificities, we would have an agreement with the clinical team to determine if they would be willing to transplant against a potentially positive flow crossmatch. We would not have been offered the second donor as the B44 would not be removed, but we would go ahead with this offer after assessing the risk.
Not enough boxes to delist in table 2. Could have included change in cRF and chance of transplant using ODT's web based tools.
It is difficult to make a scenario realistic without giving suggestions, this is a good attempt.
Interesting, well written and well presented scenario.
This is a good scenario which covers a problem often encountered in the routine setting. Though I am a little confused as to what exactly the listing criteria for assigning unacceptable is in the example given as there appears to be anomalies in the specs highlighted (DR15,16 being examples). However, overall I believe these are very useful.
As B44 is a partner mismatch, our centre would list this as an unacceptable antigen so it is unlikely our patient would have been offered this kidney. If the patient cannot tolerate enhanced immunosuppression then they should be re-entered into the next paired/pooled kidney scheme.
Would have been useful to include deadline dates for submission of update antibody information to ODT for Paired/exchange scheme purposes, especially in relation to Q4. Otherwise, interesting scenario.
We enjoyed this one. Lots to talk about and we challenged and debated our own policies.
This scenario is very challenging that unfortunately very real as we all have to deal with patients highly sensitized that stay long time in waiting list, deterioration health condition that leads to no dialysis options.
As we do not participate in paired/pooled kidney sharing scheme, we do not have the experience of this kind of scenario.
Interesting case. We were surprised that no results of CDC screening were provided. Within ET this is a mandatory test.
Very complete, close to some real life examples
The scenario is interesting as the Transplant centre that we do testing for will be starting paired transplants this year. We also do not have a policy on acceptable and unacceptable antigens at the moment and we will learn from this Scenario from the decisions that are taken in other Laboratories.
Good scenario
Classical case of transplantation risk versus mortality risk during haemodialysis and waiting list time. We have not taken the potential repeated mismatch from the patient pregnancies into account as we do not usually have access to that information in our centre.
If the patient is informed about the risk linked to a very strong immunosuppressive therapy the quality of life by being grafted allows this risk taking
Interesting.