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International Quality Expertise

Histocompatibility & Immunogenetics

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Interpretive Educational Scheme (iED)
Clinical Scenario 2/2018 – Haematopoietic Stem Cell Transplantation

Dispatched on 26th June 2018

Summary of Results

A total of 37 responses were received.

1) Comment on the likelihood of finding a HLA matched unrelated donor for this patient and any aspects of the patient's HLA type that could make the search for a donor challenging?

Responses from UK and Ireland (UK&I)

Likely to find a 10/10 matched donor
There is a high likelihood of finding a matched unrelated donor - although maybe not an optimal donor for non-HLA reasons as the number found would be quite small. Would be a challenging search due to rare/intermediate B/C association and homozygous DRB1/DQB1.
HLA-B*51:01 is associated with several different HLA-C alleles (e.g. C*01:02, C*14:02, C*15:02 and C*16:02) and is less frequently associated with C*02:02, making it less likely a 10/10 match will be found, particularly if registry HLA-C data is not provided.
HLA-C typing can be missing from some donors, this makes it difficult to predict if these donors are potentially fully matched or mismatched at HLA-C.

Responses from Rest of World (RoW)

The haplotype A*02:01 C*02:02 B*07:02 DRB1*15:01 DQB1*06:02 is not very frequent and it could represent a challenge in donor search.
The patient has a frequent HLA haplotype found in Caucasian populations with high probability to find an identical HLA 10/10 donor. The difficulty will be to find among the 30 donors 10/10 identified in the BMDW a rapidly available and CMV negative donor.
Identification of HLA matched unrelated donor could be challenging due to DRB1, -DQB1 homozygosity; HLA-B*51:01 that could be associated with different HLA-C alleles and therefore HLA-C allele MM could be expected.
The patient carries the variant HLA-B*51 that can be associated with several HLA-C alleles, but in this phenotypic context, the haplotype A24, B7, Cw7, DR15 and DQ6 is common.
Unusual HLA-B/C linkage disequilibrium (B*51:01/C*02:02): 8% (NMDP data for CAU ethnic code).

2.1) Using the information in Table 1, select three potential unrelated donors for the patient. Please provide brief reasons why the donors were selected and details of any further testing you would perform.

The following table summarises the responses given by participants for selecting donors and any further testing they would perform:

Donor	UK&I	RoW	Total	Reason for Selection	Further Testing
First Choice Donor:					
C	1	0	1 (3%)	• Likely HLA match, CMV negative.	• High resolution typing.
G	14	19	33 (89%)	• Apparent 10/10 match (high resolution). • CMV negative (match).	• High resolution typing. • DPB1 testing.

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				• Young male. • ABO match. • Reliable registry. • As HSCT is urgent, give preference to donors fully typed (also HLA-C : rare LD) in 4 digits to avoid bad surprises • DPB1 permissive.	• Re-testing of CMV. • Virology testing. • Number of transfusions.
I	0	3	3 (8%)	• 11/12 match, although DP is a mismatch is a permissive matching. • HLA high res matched, DPB1 permissive, young donor. • 10/10 allele match and permissive HLA-DPB1 mismatch. Donor age is acceptable. Female to female is ok.	• A blood subgroup typing and CMV testing. • Antibody testing of patient. • CMV. Information about weight, pregnancies and blood transfusion.
Second Choice Donor:					
A	1	0	1 (3%)	• HLA matched at high resolution at HLA-ABCDRDQ. UK donor (urgent patient; ideally receive VT samples quickly).	• Confirmatory typing. DPB1 typing if DPB1 antibodies detected in patient. Request CMV test. Patient anti-A/B titres (tested by transplant centre).
B	0	1	1 (3%)	• HLA but not CMV match but young donor.	• HRABC, DR, DQ and HLA SP and CMV.
C	1	3	4 (10.5%)	• Likely 10/10, CMV match. UK donor • Female<40 years. CMV match. Potential 10/10 match. Accredited registry.	• 2nd field typing inc HLA-C, Blood Group.
F	0	2	2 (5.5%)	• High resolution identity for HLA A, B, C, DR, DQ • ABO identical. • Donor <45 year.	• Pregnancy. • Body weight.
G	1	3	4 (10.5%)	• Known HLA match, also CMV match and ABO match	• Confirmatory typing. • Antibody screening.
H	1	0	1 (3%)	• Young male. HLA-C locus type unknown so possibility of a match.	• HLA-C SSO, then SBT if HLA-C matched, and CMV matched.
I	9	10	19 (51%)	• 10/10 high resolution match at HLA-A, B, C, DRB1 and DQB1. CMV unknown (i.e. potentially neg) younger. • DPB1* Permissive. • Alternative donor : female, CMV ? As HSCT is urgent, give preference to donors fully typed (also HLA-C : rare LD) in 4 digits.	• 2nd Field (SBT) confirmatory typing of HLA-A, B, C, DRB1, DQB1 and DPB1. • CMV and ABO. • Pregnancy. • Weight. • SAII screening.
J	2	3	5 (13.5%)	• Potential 10/10 match (low resolution). • CMV negative (match). • Male • Reliable registry. • Class I low-res match, II high-res match.	• Typing: HLA-A/B/C/DPB1 high resolution. • ABO. • Current CMV status.

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Third Choice Donor:					
A	1	3	4 (10.5%)	• HLA matched (including HLA-C). Potential CMV matched. UK donor. • High probability of 10/10 match, although ABO is not a match. • Female.	• Request VT samples (and type to high/allelic resolution for all loci including DB1). • CMV testing. • Rule out Null alleles in B locus. • Pregnancies and transfusions.
B	0	1	1 (3%)	• HLA low res matched, young, young- > probability of high res. Match high according to BMDW.	• HLA high res typing, DPB1 typing, antibody testing of patient.
C	2	3	5 (13.5%)	• Potential 10/10 match (low resolution, unknown HLA-C); CMV negative; young; adequate weight; UK registry. • HLA-DRB1, -DQB1 second field matched, HLA-A,-B antigen matched. • CMV and Sex matched.	• ABO. • CMV. • High resolution HLA typing.
F	3	7	10 (27%)	• 10/10 donor in Germany so good chance of receiving sample promptly. CMV positive donor for negative patient would be acceptable for an urgent transplant. • Backup donor: female, CMV + • As HSCT is urgent, give preference to donors fully typed (also HLA-C: rare LD) in 4 digits to avoid bad surprises.	• Verification typing. Second field class II typing, including DPB1. Second field typing for class I if this is the selected donor. • CMV and ABO. • Pregnancies and transfusions. • Weight. • Antibody screening.
H	6	2	8 (22%)	• Young male, likely HLA match, potential to be CMV/ABO matched	• ABO. • CMV. • High resolution HLA typing.
I	1	4	5 (13.5%)	• 10/10 match from Panel typing. • One mis-match DPB1 and matched for sex. • HLA match but not CMV.	• SBT if CMV matched, in the absence of a matched male. • ABO, CMV, Weight, DRB3/4/5 ad DPB1 typing. • SAII if any mismatches. • Weight and pregnancy.
J	2	2	4 (10.5%)	• Potential 10/10 high resolution match. Male, older but more likely to be HLA-C matched than donors with no C typing data. CMV unknown (potentially neg). • Potentially ABO matched. HLA matched at low resolution at HLA-ABCDRDQ. CMV matched.	• 2nd Field (SBT) typing of HLA-A, B, C, DRB1 and DQB1 and DPB1. CMV and ABO.

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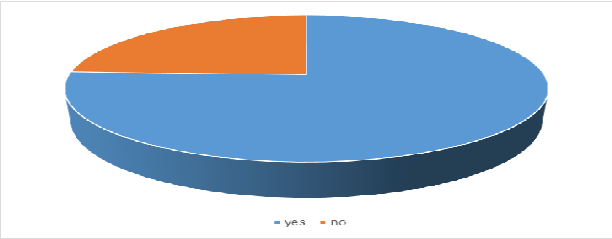
2.2) Does your laboratory test for HLA-DPB1 for HSCT patients and their donors?



	UK&I	% (n=15)	RoW	% (n=22)	Total (n=37)
Yes	10	67%	18	82%	28 (76%)
No	5	33%	4	18%	9 (24%)

Reasons from UK&I

Yes	A requirement of our transplant centre.
	DPB1 typing is routinely performed on patients and their selected donor. For urgent cases DPB1 typing is performed on all VT's requested. DPB1 typing is not used for donor selection/ranking unless there is a choice of otherwise well matched donors.
	To get best 12/12 match or to see if permissive or non-permissive.
	It helps us to decide between well matched young CMV matched donors and we can monitor any DSA present pre transplant and post transplant if required. There is published data stating better outcomes if permissive DP mismatch.
	Only if HLA-DPB1 antibodies are detected in the patient. Moving to routinely type for HLA-DPB1 in the very near future - evidence available shows strong survival advantage to using 12/12 or 10/10 with permissive DPB1 mm.
	We routinely HLA type DPB1* in patients and donors. We test all HSCT patients to see if they have HLA specific antibodies including those directed against HLA-DPB1*. We use the DPB1* T cell epitope algorithm for patients and potential donors.
	Yes- HLA-DPB1 has been shown to be important for stem cell transplant outcomes (Shaw et al., 2010). Typing for HLA-DPB1 is recommend by BSHI guidelines (Little et al., 2016)
	We test for HLA- DPB for HSCT patient going to have an unrelated donor search. We do not type related donors for HLA-DPB and we do not receive samples from unrelated donor searches.
No	We do not perform HPCT HLA typing; if we did we would HLA-DPB1 type patients/donors.
	Not currently part of protocol agreed with clinicians.
	Patients and donors will be able to be routinely DPB1 typed following the introduction of NGS. Currently in discussion with transplant centres as to how to use this data.

Reasons from RoW

Yes	This analysis is not yet requested routenely by the in the Bone Marrow Transplant Service of our area, but we have a Sanger SBT kit to do the analysis and we perform upon request.
	Total number of mismatches impact the risk of GvH and overall survival is better in case of no non-permissive HLA-DPB1* mismatch. Moreover, allosensitization against donor DPB1 antigen can delay engraftment.
	Many studies have shown the relevance of HLA -DPB1 matching in HSCT. We test for HLA-DPB1 especially in case of several 10/10 HLA matched donors in order to choose the best one.
	To find permissive mis-matches and to avoid antigens with DSA.
	In order to predict GVH responses and to select the best donor within HLA matched ones and to eliminate a "non permissive, HvG " donor to prevent graft failure.

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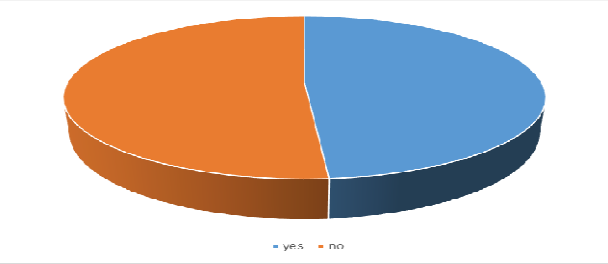
	We try to find better matched donor for all of the HLA loci. HLA-DPB1 match is specially searched for HSCT Class 1 mismatched graft.
	Additional risk calculation after considering HLA 10/10 2nd field match, CMV match, ABO match and donor sex/age. Permissive in GvH direction has priority on non-permissive mismatch in GvH.
	Because of the prevalence of HLA DP antibodies.
	A multi-centric French study has shown that double DPB1 mismatch comes with higher risk of acute GVHD.
No	Not mandatory for transplant.
	HLA-DPB1 typing will be introduced in near future.
	Not currently part of TC protocol. Currently being validated in some laboratories.

2.3) Does your laboratory report permissive/non-permissive DPB1 mismatch information?



	UK&I	Percentage (n=15)	RoW	Percentage (n=22)	Total (n=37)
Yes	6	40%	12	54.5%	18 (49%)
No	9	60%	10	45.5%	19 (51%)

Reasons from UK&I

Yes	To the clinicians on the HLA typing report and at the MDT for each patient.
	There is evidence in current literature that supports HLA-DP matching and use of the permissive/ non -permissive DPB1* T cell epitope algorithm. This literature suggests DPB1* matching and choosing permissive DPB1* mismatched donors leads to improved transplant outcome in HSCT.
	It is not always possible to find donors matched at HLA-A,B,C,DRB1,DQB1 and HLA-DPB1 (a 12/12 match). It has been shown that some DPB1 share T cell epitopes therefore you can select donors which match the patient for these T cell epitopes, this is called permissible mismatch and has been shown to have better outcomes post stem cell transplant (Fleischhauer et al., 2012 & Crivello et al., 2014).
	Published evidence from a UK cohort should a 12/12 donor not be found our centres will use permissive and non-permissive in their final donor selection choices.
No	Not currently part of protocol agreed with clinicians.
	There is less compelling data demonstrating the impact of DPB1 permissive/non-permissive matching compared to other factors (i.e. HLA/CMV/age/sex/ABO etc.) Our donor selection is prioritised based on factors that are well documented as impacting on patient outcome.
	Not currently reported on the laboratory HLA typing reports but is discussed in meetings with transplant teams. It is a factor in donor selection for some patients.
	Not at present, but we will be incorporating this into our new algorithms as a result of our change in typing methodology.

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Reasons from RoW

Yes	This information allows the clinician to better select the unrelated donor according to the patient's pathology and the stage of his disease.
	Data from many studies shoving the effect of permissive and non -permissive DPB1 matching. In most of the cases we are not able to find HLA-DPB1 second filed matched unrelated donor and the option would be to select donor with permissive HLA-DPB1 MM.
	In order to predict GVH responses and to select the best donor within HLA matched ones and to eliminate a "non permissive, HvG " donor to prevent graft failure.
	DPB1 is difficult for allele matching, priority matching on DPB1 TCE groups. We discuss the TCE groups with the clinic, this allows them to take TCE matching into account.
	To inform with the risk of GvH or HvG.
	Clinical interest.
	Requested by clinician to find a DPB1 permissive donor when possible.
	Our donor selection algorithm is 1) 10/10 allele match donor; 2) HLA-DP matched donor or HLA-DP permissive mismatch; 3) Donor age; 4) CMV and AB0. Data is discrepant on the relative importance of sex and CMV: NMDP no importance, EBMT sex is important; British data CMV is important. Everybody agrees on HLA matching and donor age.
No	We do not yet do this analysis routinely; probably we will in a near future and we will give this information in the laboratory report.
	The information is not given to clinicians but it is noted in the files.
	Current literature regarding overall survival are contradictory about DPB1 mismatch and TCE influence.
	Often not enough time, not enough donors, to consider DPB in the choice.
	Not currently considered but we should.

3) Using the additional information, rank donors K, L and M in order of preference and outline your reasons for selection.

		First Choice	Total	Second Choice	Total	Third Choice	Total
K	**UK&I**	**5**	**9**	**8**	**19**	**5**	**12**
	RoW	**4**	**(24%)**	**11**	**(51%)**	**7**	**(32%)**
L	**UK&I**	**0**	**1**	**5**	**14**	**10**	**22**
	RoW	**1**	**(3%)**	**9**	**(38%)**	**12**	**(60%)**
M	**UK&I**	**10**	**27**	**2**	**4**	**0**	**3**
	RoW	**17**	**(73%)**	**2**	**(11%)**	**3**	**(8%)**

UK&I		
Donor	**Reason for Selection**	**DPB1 information that would be provided to Clinical Team**
K	• Male; youngest donor; ABO match; non-permissive in HvG but rejection a rare occurrence. • Younger male donor preferred. Better data on age and gender impact on survival versus DP permissive/non permissive matching. • The transplant centre is likely to select this fairly young man despite the non-permissive DPB1 mismatch. • Youngest donor, male, Non permissive DPB1 mm in the HvG direction.	• Non permissive. • HLA-DPB1 type. • The number of allele mismatches is included in the report comments. Discussions about potential donors would include permissive/non-permissive mismatches. • DPB1 predicted immunogenicity: Non-Permissive HvG. • HLA antibody results required to ensure no

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	• Non-permissive HVG, high immunogenicity for DP9.	donor directed HLA-DP antibodies. • GvHmm = 2DP (0/10, 2/12) DPB1 mismatch is non-permissive. • 10/12 non permissive HvG HLA- DPB1 mismatch.
L	• ABO match; low immunogenicity in GvH will contribute to GvL and decrease risk of relapse. • Non-permissive mm but may be chose to promote the GvL effect (important in high-risk ALL as in this case). • Non-permissve GVH and possible GVL, Low immunogenicity. • Oldest female donor, Non permissive DPB1 mm GvH, 10/12mm. • Non-permissive DPB1 mismatch in the GvH direction. This may have a higher risk of GvHD and TRM. • Older female, could have had pregnancies - increased risk of GVHD despite being permissive DP matching.	• Non-permissive. • 10/12 non permissive GvH HLA-DPB1 mismatch. • GvHmm = 2DP (0/10, 2/12) DPB1 mismatch is non-permissive • Non permissive HLA-DPB1 mismatch in the GvH direction. HLA antibody results required to ensure no donor directed HLA-DP antibodies.
M	• DPB1 permissive. No pregnancies. No transfusions. • 11/12 Match. • Young donor. • Preferred over ABO compatible or DP permissively matched donor. • ABO mismatch; ABO match ranked more highly than permissive/non-permissive DPB1 mismatch.	• DPB1 predicted immunogenicity: Permissive. • 11/12 mm, permissive DPB1. • Permissive HLA-DPB1 mismatch in both the GvH and HvG direction. HLA antibody results required to • Ensure no donor directed HLA-DP antibodies. • GvHmm = 1DP (0/10, 1/12) DPB1 mismatch is permissive. • The number of allele mismatches is included in the report comments. Discussions about potential donors would include permissive/non-permissive mismatches.
RoW		
K	• ABO identical, non-permissive in GvH direction absent, young male, ABO identical. • Young male donor, ABO matched. • Non permissive HvG HLA-DP mismatch is preferred to non-permissive GvH mismatch. • Male donor, HLA 10/12. • All donors have equivalent age and are CMV matched. • It is a non-permissive DPB1 matching in HvG direction, with high risk. • It is a non-permissive DPB1 matching in HvG direction, with high risk. • Gender, ABO compatibility, The titer of anti DPB1 13:01 is not so high in our patient the pirche score is low(2). • ABO type is matched, DPB1 matching is non-permissive HvG. Donor is TCE group 1/3, patiënt is TCE group 2/3.	• Antibody testing with SAB required • non-Permissive HvG. • 10/12 matched donor with non permissive HvG mismatch. • 2 DPB1 mismatches (we should add: "non permissive HvG mismatch"). • Non permissive DPB1 mismatch in HVG direction. • DPB1*09:01,*13:01 non permissive HvG. • Non-permissive DP match according to Zino et al. • The donor and recipient share only one HLA-DPB1 alelle. The DPB1 mismatch of the donor (DPB1*09:01) is considered highy immunogenetic and is considered to be non-permissive in HvG by Crocchiolo et al. • High risk of TRM and graft failure. • TCE group mismatched in the HvG direction.
L	• ABO type is matched, DPB1 matching is non-permissive GvH, which can give GvL. Donor is TCE group 3/3,	• TCE group mismatched in the GvH direction.

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	patient is TCE group 2/3. • DPB1 low expression. • Young female donor, HLA 10/10 match, CMV match. • ABO matched. • ABO compatible, we do not expect for anti HLA-ABCDRDQ antibodies against the patient The titer of anti DPB1 13:01 is not so high in our patient the pirche score is low(5). • Gender matched donor, HLA 10/10 matching, DPB1 non-permissive MM GvH and therefore GvL effect could also be expected. • Donor 10/12 (10/10 with two mismatch DPB1), matched for ABO, but no information for pregnancies or transfusions.	• DP TCE non-permissive mismatch (low expression). • Antibody testing with SAB required Non-permissive GvH. • An increased risk for a GVHD and TRM. • Presence of non-permissive HLA- DPB1 MM in GvH direction. • The donor and recipient do not share any HLA-DPB1 allele. This mismatch was proposed to be non-permissive in GvH direction by Crocchiolo et al. • Non-permissive DP match according to Zino et al. • Two mismatch DPB1 non permissive with risk of GvH.
M	• Permissive mismatch. • Donor 11/12 (10/10 with one mismatch DPB1), matched for sex ; no pregnancies or transfusions. • HLA -10/10 matching, permissive HLA-DPB1 MM, CMV negative, no pregnancies and transfusions and therefore low risk of sensitization. • Even ABO incompatibility (RBC depletion suggested) we do not expect for anti HLA-ABCDRDQ abs directed to the patient A permissive mm for DPB, pirche score not high (=3). • Young female, no pregnancies, no transfusions, permissive DPB1. • Best match (HLA 11/12), female but no pregnancies. • All donors have equivalent age and are CMV matched. • Permissive HLA-DPB1 mismatch is preferred from non-permissive mismatches. ABO, donor sex and age have lower priorities in our donor selection algorithms. • One DP allele identical, other with low immunogenicity. • ABO type is mismatched, but DPB TCE group is matched (permissive).	• The donor and recipient share only one HLA-DPB1 allele. The DPB1 mismatch phenotype of the donor wasproposed to be permissive by Crocchiolo et al. • One mismatch DPB1 permissive. • Permissive DP match according to Zino et al. • A permissive MM, expectation for a decreased relapse risk. • The pair DPB1*02:01, *03:01 is mismatch permissive. • DPB1*02:01,*03:01 permissive mismatch. • DP TCE permissive mismatch. • 1 DPB1 mismatch (we should add :"permissive mismatch"). • TCE group is matched with the patient. • Antibody testing with SAB required. • 11/12 matched donor with DPB1 permissive mismatch.

4) Has the HLA antibody data in Table 3 affected the order of donor preference as indicated when answering Q3?

	UK&I	Percentage (n=15)	RoW	Percentage (n=22)	Total (n=37)
Yes	7	47%	16	73%	23 (62%)
No	7	47%	5	23%	12 (33%)
No Answer	1	6%	1	4%	2 (5%)

Interestingly, of those that replied No some justified their decision with comments including:

- Lack of evidence of clinical significance of MFI value for DPB1 antibody in HSCT.

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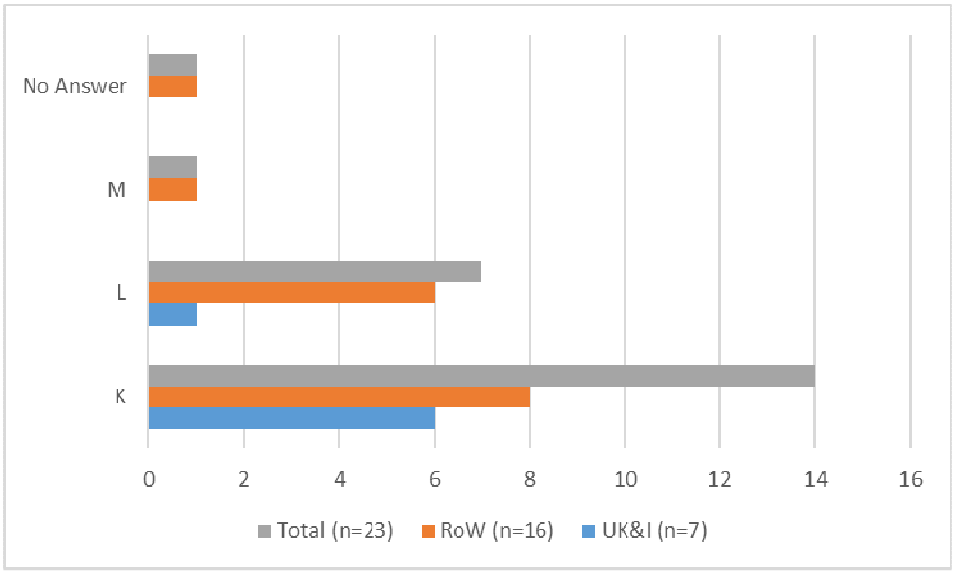
- Approach was to ascertain mean MFI for each specificity and determine cumulative MFI against donor DPB1 mismatch. Low risk of DPB1*13:01 mismatch at 2301 [mean] MFI; beads have an increased antigen load versus cells.
- Patient has HLA-DPB1*02:01 donor specific antibodies to donor M, but with an MFI of 6428 so considered relatively low. A crossmatch could be carried out prior to transplant to help fully evaluate the risk associated.
- Although the DPB1 antibody would be considered, there is no published evidence that selecting an additional mismatched donor in the context of antibodies at this level would be beneficial. Options including further monitoring, crossmatching or antibody removal would be discussed.
- Because the patient has antibodies against both DP2 and DP13 and DP2 has lower expression level.
- Donors K and L are still the best donors since the patient displayed anti DPB1*0201 (MFI 6428) against donor M whereas the MFI of anti DPB1*13:01 is only 2532.

If yes, which donor would now be your first choice (K, L or M)?

Donor	UK&I (n=7)	RoW (n=16)	Total (n=23)
K	6	8	14 (61%)
L	1	6	7 (31%)
M	0	1	1 (4%)
No Answer	0	1	1 (4%)



Reasons from UK&I

K	Hasn't affected selection. Lowest Antibody levels by Luminex SA.
	Due to lower antibody level combined with host vs. graft DP permissive.
	M is positive for DP2, the patient has an antibody MFI 6428 would be moved to the bottom. K and L are positive for DP13, the patient has an antibody MFI 1986. A study showed MFI>5000 and C1q pos poor engraftment however little evidence to support MFI values and engraftment. Some labs might do a crossmatch, DP not expressed on stem cells however if there was a choice we would avoid DSA with MFI>5000.
	No antibodies against the original first choice. Transplant team might be nervous about the higher MFI antibody against DP2 and make L the second choice.
	Patient has a DPB1*02:01 DSA against donor M (with an MFI of 6428) which may increase the risk

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	of rejection; therefore donor M would be avoided. K and L both have DSAs with lower MFIs which are unlikely to have an effect. K is male and younger than L. If taking DPB1 matching into account, K has a non-permissive DPB1 mismatch in the HvG direction which my be favourable over L, which has a non-permissive DPB1 mismatch in the GvH direction.
	Although role of HLA-DPB1 antibodies has not been established in context of 10/10 match stem cell transplant whilst the role of HLA-DPB1 permissive mismatches has evidence to support avoiding non permissive mismatches, the DSA is above 5000. In addition, donor K is a younger male and is blood group matched as opposed to the major blood group mismatch of donor M.
	Presence of high MFI DSA in donor M could potentially lead to non-engraftment.
L	The patient has antibodies to HLA-DP2 with MFI 6428 against donor M. Due to this donor L would be our first choice.

Reasons from RoW

K	Recipient has anti-DPB*02:01 (DSA against M with MFI 6428) and anti-DPB1*13:01 against K and L (MFI 2385). So we eliminate M and we choice K (ABO match).
	K donor is preferred due to moderate intensity of HLA DPB1-*13 Ab compared to HLA DPB1-*02 Ab. Because we have no information about pregnancies of donor L and because K donor has the same blood group, we choose this donor.
	The patient has antibodies against both DP2+13 on donor M that has a permissive mis-match. The pattern of reactivity is however, not easily explained by epitopes thus looking for DPA1 reactivity, thus having both patient and donors typed for DPA1 could help to interpret results.
	Donor M specific antibodies anti-DP2>5000. Presence of DSA anti-DP13 for donor K and L but with a MFI below 5000.
	HLA Ab against DP2 and MFI quite high (> 5000).If possible we'll perform a cross-match (but if CMF negative, the M donor could maybe be chosen). Otherwise, the K donor will be choose, although there are some Ab against DP13, but MFI are quite low and L Donor (older than K donor) is also DP13
L	There is not anti HLA-ABCDRDQ abs directed to the patient, the titer of anti DPB1 is not so high, A non permissive mm for DPB unfortunately with the expectation for an increased risk of TRM, and aGVHD, Pirche score not very high (=5).
	Order has changed, but not the first choice. We would not call donor M for donation, because there are antibodies with MFI > 4000. We would inform the clinic that there are antibodies with MFI between 1000 - 4000 against donors L and K. Antibody profile on DP has been checked for epitope reactivity. No epitope can be identified.
	We exclude donors with high risk regarding DSA if alternate donors are available. [no risk : MFI < 1 000 ; low risk : 1000 < MFI < 5000 (and cross match FACS - and cytotoxic -) ; medium risk : 5000 < MFI < 10 000 (with cross match FACS + but cytotoxic -) ; high risk : MFI > 10 000 (cross match FACS + and cytotoxic +). Crossmatch data is not available in this scenario.
	MFI against DPB1*13:01 (2532) is significantly lower than against DPB1*02:01 (6428) - preference against donor M. Non-permissive immunogenicity GvH is preferred than HvG - preference against donor K.
	All match factors remain the same, however, L has a lower MFI than the other donors.
M	Due to the weak expression of DPB1 antigens, the presence of anti-DPB1 antibodies is not taken into account.
No Answer	Antibodies with MFI>2000 are a contraindication for donor selection; only in case of no further donors available, antibody removal strategies are considered. Then we would take the donor with lowest MFI values.

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5) The transplant goes ahead with the donor of your choice, please state what follow-up/post transplant testing you would recommend and why?

UK&I	Monitor post-transplant CII antibodies (Single Antigen CII); impact of DP1*13:01 donor-specific antibody? Chimerism monitoring: detect rejection and relapse. Ascertain whether B/T-ALL to monitor appropriate lineage.
	Chimerism testing for monitoring of engraftment/disease relapse.
	Single antigen testing if required by transplant team.
	Chimerism analysis and MRD testing at months 1, 2, 3, 6, 12 post transplant and annually thereafter. More frequent monitoring is performed if any problems. FISH used for chimerism testing if sex mismatched, microsatellites used for sex matched pairs.
	As high risk ALL would also test to ensure no relapse of disease.
	Chimerism for post-transplant monitoring (at 28 days then weekly for 1 month, monthly for 6 months then at less frequency). HLA antibody screen should be performed at these intervals also to ensure DSA levels are monitored (could lead to delayed engraftment).
	Post transplant monitoring would include chimerism testing at 4, 8, 12, 52 weeks then annually. Possible post transplant DSA as required clinically.
RoW	Engraftment monitoring with chimerism, white blood cells count and follow-up of DSA levels (HLA-DPB1*).
	The follow-up would include: Chimerism monitoring, immunophenotyping, monitoring of MRD, alloantibody testing, virological monitoring, Immunoglobulins, TREG.
	Chimerism tests, Blood group typing, detection for anti HLA abs (Single bead).
	Monitoring of HLA DPB1 antibody and its ability to fix complement if MFI>3000 (C1q assay).
	Search for new donors.
	Chimerism testing on CD3 cellular subset.
	Chimerism at D21-30, M2, M3, HLA antibody

Any other comments?

UK&I	More compelling data is needed on the impact of DSA and DPB1 permissive/non permissive matching in HSCT before incorporating into routine donor selection practice. Currently, we would not consider the presence of an non-permissive DPB1 mismatch or HLA-Class II DSA a barrier to selection of an otherwise well matched donor. However, following discussion of this case we plan to use the DPB1 T-Cell Epitope Algorithm tool and discuss the findings at MDT for information/training purposes.
	Locally any antibody over 1000MFI is a relative contraindication to transplant requiring clinical intervention before proceeding with transplant.
	As the patient is urgent may consider haplo from one of the half siblings for speed? Also we would have chosen 4 donors to further investigate in question 1 (also donor C as UK CMV matched donor).
	H&I staff select the donors for VT but do not make the final donor selection. The donor for work-up is selected by the transplant team with input from H&I.
	Importance of HLA antibody testing prior to donor selection. Importance of sequential antibody screening and testing of a current sample. Transfusion information should be provided by the clinical team. May choose to KIR genotype the unrelated donors to identify a KIR B haplotype donor in accordance with KIR B content scoring model (Cooley et al, 2010).
	The answers to question 3 are based on the data provided in Table 2 and the DPB1 T cell epitope

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	algorithm results. This is not an approach we use in our laboratory so we assessed this based on the data provided rather than using our normal approach. Answers to all other questions are based on our normal approach.
	Given the original situation was described as "urgent" we would order more that 3 VTs. A time to transplant would have been useful to understand the urgency which may have changed our options.
RoW	Because of the graft emergency, we could not carry on - a FCXM predictive of level of risk of HLA-DPB1*02:01 for K donor (with a FCXM neg, maybe we could accept this donor) - plasmapheresis to eluate HLA-DPB1*02:01 it would be important to test female donors for HLA-Ab to evaluate impact on platelet transfusion after graft.
	Antibodies against DPB1*13:01 were three times included into Table 3. We evaluated this like a mistake and ignored the results with lower MFI.
	Pre-transplant: Screen donor for HLA Ab's. Monitor titre in patient; If titre rises, consider TPE.