UK NEQAS
International Quality Expertise

Histocompatibility & Immunogenetics

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Interpretive Educational Scheme (iED)
Clinical Scenario 1/2019 – Renal Transplantation

Dispatched on 21st May 2019

Summary of Results

A total of 53 responses were received, 23 from UK & Ireland (UK&I), 30 from Rest of the World (RoW).

1. **Patient X is referred to your laboratory to be activated in the deceased donor transplant list having been previously transplanted at another centre. What testing do you perform prior to activating the patient on the transplant list?**

Some of the most common responses included:

Response	Number of Labs (n=53)
Perform additional/repeat antibody testing	46
Confirm patient HLA type/perform additional typing/higher resolution	38
HLA type previous donors/additional loci/higher resolution	20
Request antibody test results / sera from other centre	17
Perform autologous crossmatch	7
Confirm ABO	6

Other selected comments
• Accept previous typing and antibody results if EFI accredited lab • Request previous sera from other centre and retest Luminex single antigen as MFI values/cut offs vary between centres. • 2x HLA antibody screening; given the unusual antibody profile which includes allelic and auto antibodies • Full HLA type of patient's wife (confirm unusual associations of DR4 with DQ9 & B7 & B8 with Cw2 & Cw3)

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What specificities, if any, would you list as 'unacceptable antigens'? Please detail the specificities that you would recommend for listing with reasons:

HLA Spec	Number of labs agreeing to list Spec			Reason(s) for listing as unacceptable antigen
	Total (n=53)	UK&I (n=23)	RoW (n=30)	
None	5	4	1	No unacceptable antigens
DR9 / DRB1*09:01	37	16	21	MFI >1000/>1500/>2000/>2500/>3000/>4000/ Previous Mismatch
DR7 / DRB1*07:01	37	18	19	MFI >1500/>2000/>3000 Previous Mismatch
DR15 / DRB1*15:01	31	9	22	MFI >1000/>2000 Previous mismatch
DR17 / DRB1*03:01	29	11	18	MFI >1000/>2000 Previous Mismatch
DP23 / DPB1*23:01	27	15	12	MFI >1000/>1500/>2000
DP14 / DPB1*14:01	26	13	13	MFI >1000/>1500/>2000
DR10 / DRB1*10:01	26	11	15	MFI >1000/>1500/>2000 Previous Mismatch
DR8 / DRB1*08:01	22	8	14	MFI >1500/>2000
DP4 / DPB1*04:01	21	10	11	MFI >1000/>1500/>2000
DR13 / DRB1*13:01	21	7	14	MFI >1000/>1500/>2000
DR51 / DRB5	20	7	13	MFI >2000 Previous mismatch
DR12 / DRB1*12:01	19	6	13	MFI >1000/>1500/>2000 Previous Mismatch
DR103 / DRB1*01:03	18	11	7	MFI >1000/>2000 Previous mismatch
DR14 / DRB1*14:01	17	4	13	MFI >1000/>1500/>2000
DR1 / DRB1*01:01	17	3	14	MFI>2000
DR16 / DRB1*16:01	16	2	14	MFI >1500/>2000
DR52 / DRB3	14	5	9	MFI >1500/>2000
B8	11	6	5	MFI>2000 Previous mismatch
A30	9	6	3	MFI>2000 Previous mismatch
DQ9	7	4	3	Previous mismatch
DQ2	7	4	3	Previous mismatch
DQ6	6	3	3	Previous mismatch
Cw3	6	4	2	MFI>2000 Previous mismatch

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A1	6	3	3	Previous mismatch
A11	3	0	3	MFI > 1000
DR4	3	0	3	MFI >2000
DR3	2	1	1	Previous mismatch
DR18	2	0	2	Associated with DRB3*01:01 MFI >2000 Previous mismatch
DQ1	1	1	0	Previous mismatch
DR2	1	1	0	Previous mismatch
DRB4	1	0	1	MFI
All MFIs >1000	1	0	1	
All with consistently raised MFIs	1	0	1	

UK NEQAS for H&I Comments

There was a range of unacceptable antigens listed for this patient. 5 centres stated they would list no unacceptable antigens, while the remainder would list between 2-24 (mean 9.7). These differences could mean the patient was listed with a calculated reaction frequency (cRF) of between 0- 95%, depending on the centre. *(NHSBT ODT Calculated reaction frequency tool https://www.odt.nhs.uk/transplantation/tools-policies-and-guidance/calculators/)*

Some of the differences could be due to a centres policy on listing previous transplant mismatches as unacceptable antigens. Some centres appear to have a policy to list all previous transplant mismatches, while others only if antibodies to the mismatches were detected.

There was also variation in the nomenclature used to list the antigens that would be listed as unacceptable for transplant. Some labs listed the alleles represented on the single antigen bead rather than the specificity (e.g. DRB1*03:01 versus DR17; DRB5 versus DR51).

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	Total (n=53)	UK&I (n=23)	RoW (n=30)
Yes	42 (79.2%)	20 (87.0%)	22 (73.3%)
No	11 (20.8%)	3 (13.0%)	8 (26.7%)

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If Yes, please give detail: Selected comments

Investigate alternative living donors and national kidney sharing scheme.
Investigate high reactivity of sera e.g. DSA pre-adsorption; denatured antigen reactivity
cRF is high, consider increasing MFI threshold to 2000 for HLA A, B, DR and DQ and 3000 for DPB1 and Cw for UAG listing (or higher) to increase chance of offer
Could perform Luminex antibody testing with another kit to confirm/rule out non-specific reactivity, as antibodies detected against patients own type
Not used routinely at present but we could use C3d kits to determine if any of the antibodies could fix complement.
Supplementary HLA typing of previous donors (DPB1, DRB3 and DRB5 typing of the heart donor. DPB1 typing and DRB1*04 subtyping of kidney donor) to ascertain if Luminex reactivity is donor specific.
Treat serum with EDTA to remove any prozone effect.
We would discuss the clinical urgency of this case and de-list specificities if advised
Advisable to confirm risk of delisting DR7 by performing a third party crossmatch
Labscreen C1q testing.
Split Cw3 type of pervious kidney donor so as only to list actual mismatches. DP type patient and LR kidney donor
Retype the patient's kidney donor. The reported HLA-DR4 - -DQ7, -DQ9 is an unusual association. Confirm whether the donor is DR4 only. HLA-DQ9 is usually found with HLA-DR7 or HLA-DR9.
If patient fit for enhanced immunosuppression then review list of unacceptable antigens.
Identify reasons for loss of 1st renal graft, whether thrombosis was surgical, inflammatory or immunologically related
Perform autologous XM to aid with interpretation of any subsequent allo-XM.
Consider de-listing previously mismatched antigens after 2 years, if antibodies to these antigens have not been detected.
We would perform the HLA Matchmaker algorithm and Pirche program using the two previous donors' HLA.

3. **Would this transplant proceed based on a virtual crossmatch in your laboratory?**

Decision	Total (n=53)	UK&I (n=23)	RoW (n=30)
Yes	8 (15.1%)	2 (8.7%)	6 (20.0%)
No	45 (84.9%)	21 (91.3%)	24 (80.0%)

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4. **What pre-transplant testing would you perform?**

	Total (n=53)	UK&I	RoW
CDC XM & FCXM	26 (49.1%)	11	15
CDC XM only	12 (22.6%)	0	12
FCXM Only	12 (22.6%)	11	1
Luminex AB Screen	21 (39.6%)	9	12
HLA Type	24 (45.3%)	7	17
Other	8 (15.1%)	3	5

Other:

- Confirmatory Blood Group
- Class I serological typing of the donor
- Allelic HLA type
- C1q

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?**

		Total	**UK&I**	**RoW**
CDC	**Positive**	1 (1.9%)	0	1 (3.3%)
	Negative	46 (86.8%)	18 (78.3%)	28 (93.3%)
	Other	3 (5.7%)	3 (13.0%)	0
	N/A	3 (5.7%)	2 (8.7)	1 (3.3%)
Flow Cytometry	**Positive**	9 (17.0%)	1 (4.3%)	8 (26.7%)
	Negative	21 (39.6%)	10 (43.5%)	11 (36.7%)
	Other	17	10	7
	N/A	6		

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6. **Based on your predicted crossmatch result, what level of immunological risk would you assign to this transplant?**

	UK&I (n=23)	RoW (n=30)	Total (n=53)
Standard	8 (34.8%)	1 (3.3%)	9 (17.0%)
Low	3 (13.0%)	3 (10.0%)	6 (11.3%)
Intermediate	8 (34.8%)	17 (56.7%)	25 (47.2%)
High	1 (4.3%)	3 (10.0%)	4 (7.5%)
Contraindication	0	4 (13.3%)	4 (7.5%)
Other	3 (13.0%)	2 (6.7%)	5 (9.4%)

Comments from the Steering Committee Member who set the scenario:

This scenario was based on a real case. I picked it as I was interested to see if others would approach it differently especially in terms of dealing with a patient with a complex transplant history and an antibody profile which includes self-reactivity. It was fascinating to note the differences in the listing of unacceptable antigens and the divergent approach to the inclusion of previous mismatches. Likewise, the use of virtual crossmatching was thought-provoking and the variations in policies for patients who are sensitised (HLA-DPB1*04:01 donor specific antibody present in this case) this implies.

It was interesting to note that the type of pre-transplant testing performed differs not only within the UK&I with around half of labs using a CDCXM in combination with a FCXM. In the ROW replies, 12 labs only use CDCXM. It was also interesting to note that 40% of respondents also performed antibody screening in an on-call setting. Labs seem to have a good understanding of how results correlate to expected outcomes and risk stratifications.

Patient Follow Up

The patient received an altruistic donor transplant in March 2019, a 211 mismatch grade. The patient had some inconsistent donor specific antibody to A2, DR13 and potential DR52 and DR53. The CDC crossmatch was negative and flow cytometry crossmatch was positive, but the autologous flow cytometry crossmatch was also positive. Given the patients complex antibody profile, self-reactivity, waiting time, and limited other live donor options, the decision was made to proceed with the transplant. A borderline rejection episode was noted, but the graft is still functioning and patient is doing well post transplant.