UK NEQAS Histocompatibility & Immunogenetics

UK NEQAS H&I

Educational Scheme (iED) Scenario 2: HSCT Scenario Feedback

@UKneqasHI

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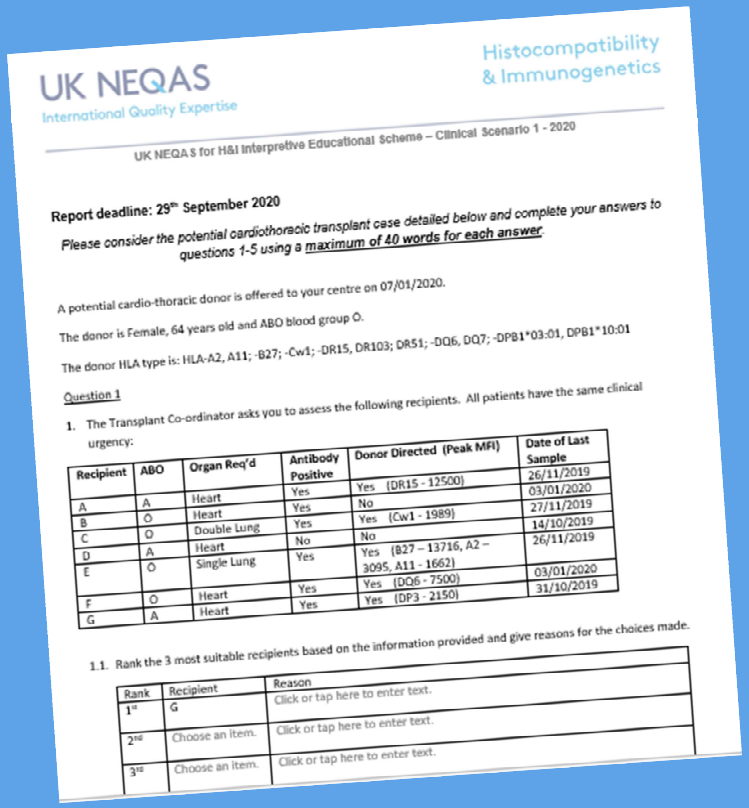
Our iED Schemes



UK NEQAS
International Quality Expertise

Histocompatibility & Immunogenetics

UK NEQAS for H&I Interpretive Educational Scheme – Clinical Scenario 1 - 2020

Report deadline: 29th September 2020

Please consider the potential cardiothoracic transplant case detailed below and complete your answers to questions 1-5 using a maximum of 40 words for each answer.

A potential cardio-thoracic donor is offered to your centre on 07/01/2020.

The donor is Female, 64 years old and ABO blood group O.

The donor HLA type is: HLA-A2, A11; -B27; -Cw1; -DR15, DR103; DR51; -DQ6, DQ7; -DPB1*03:01, DPB1*10:01

Question 1

1. The Transplant Co-ordinator asks you to assess the following recipients. All patients have the same clinical urgency:

Recipient	ABO	Organ Req'd	Antibody Positive	Donor Directed (Peak MFI)	Date of Last Sample
A	A	Heart	Yes	Yes (DR15 - 12500)	26/11/2019
B	O	Heart	Yes	No	03/01/2020
C	O	Double Lung	Yes	Yes (Cw1 - 1989)	27/11/2019
D	A	Heart	No	No	14/10/2019
E	O	Single Lung	Yes	Yes (B27 – 13716, A2 – 3095, A11 - 1662)	26/11/2019
F	O	Heart	Yes	Yes (DQ6 - 7500)	03/01/2020
G	A	Heart	Yes	Yes (DP3 - 2150)	31/10/2019

1.1. Rank the 3 most suitable recipients based on the information provided and give reasons for the choices made.

Rank	Recipient	Reason
1st	G	Click or tap here to enter text.
2nd	Choose an item.	Click or tap here to enter text.
3rd	Choose an item.	Click or tap here to enter text.

- 3 clinical scenarios a year
  - Solid organ, HSCT, platelet/transfusion
- Based on patient cases
  - Provide relevant clinical details and test results
  - Questions on interpretation of results and clinical advice
- Not assessed
- Provided free of charge

HSCT Scenarios

Year	HSCT Scenario Theme	Returns
2013	Matched unrelated donor	27
2014	Mismatched unrelated donor	42
2015	Paediatric cord donor selection	43
2016	Donor search for patient with unusual HLA type	45
2017	Haploidentical donor selection	49
2018	Unrelated donor selection – permissive/non-permissive options	37
2019	Haploidentical donor selection with antibody	50
2020	MUD, Cord or haplo donor selection	49
2021	Haploidentical transplant with Loss of Heterozygosity	47

- Dispatched on 30th August 2022
- 39 Responses
  - 14 from UK and Ireland (UK&I)
  - 25 from the Rest of the World (RoW)

Case History

A 47 year old male patient diagnosed with Myelodysplastic Syndrome (MDS)

Patient's HLA type:

HLA-A*01:01, A*26:01; B*07:02, B*38:01; C*07:02, C*12:03; DRB1*11:01, DRB1*15:01; DQB1*03:01, DQB1*06:02; DPB1*04:01, DPB1*-

ABO group: O+

CMV: positive

The patient has 2 siblings:

Sibling 1 - Sister 49 years				**Sibling 2** - Brother 52 years		
HLA-A	A*01:01	A*02:01		HLA-A	A*01:01	A*02:01
HLA-B	B*07:02	B*44:02		HLA-B	B*08:01	B*44:02
HLA-C	C*05:01	C*07:02		HLA-C	C*05:01	C*07:01
HLA-DRB1	DRB1*01:01	DRB1*11:01		HLA-DRB1	DRB1*01:01	DRB1*04:01
HLA-DQB1	DQB1*03:01	DQB1*05:01		HLA-DQB1	DQB1*03:01	DQB1*05:01
HLA-DPB1	DPB1*04:01	-		HLA-DPB1	DPB1*03:01	DPB1*04:01

**Mismatches have been highlighted in red*

Case History

An search for an unrelated donor was also carried out and confirmatory samples were requested from the following donors:

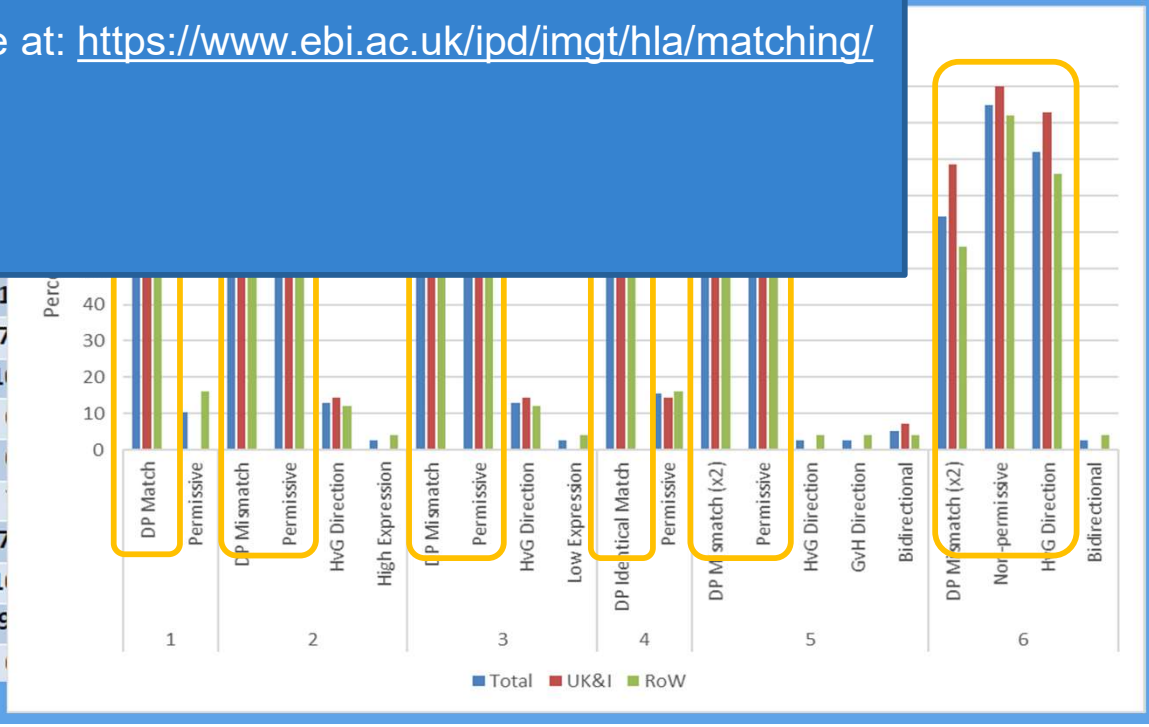
Donor Number and Registry	Sex	Age	Blood group	CMV	HLA-A	HLA-B	HLA-C	HLA-DRB1	HLA-DQB1	HLA-DPB1
Patient	***M***	***47***	***O+***	***Pos***	***01:01 26:01***	***07:02 38:01***	***07:02 12:03***	***11:01 15:01***	***03:01 06:02***	***04:01***
Donor 1 Germany	M	23	A+	neg	01:01 26:01	07:02 38:01	07:02 12:03	11:01 15:01	03:01 06:02	04:01
Donor 2 Germany	M	27	A+	pos	01:01 26:01	07:02 38:01	07:02 12:03	11:01 15:01	03:01 06:02	01:01 04:01
Donor 3 Austria	M	23	B+	pos	01:01 26:01	07:02 38:01	07:02 12:03	11:01 15:01	03:01 06:02	02:01 04:01
Donor 4 UK	F	23	O+	pos	01:01 26:01	07:02 38:01	07:02 12:03	11:01 15:01	03:01 06:02	04:01
Donor 5 UK	M	47	O+	pos	01:01 26:01	07:02 38:01	07:02 12:03	11:01 15:01	03:01 06:02	01:01 02:01
Donor 6 Germany	M	33	O+	pos	01:01 26:01	07:02 38:01	07:02 12:03	11:01 15:01	03:01 06:02	03:01 09:01

Q1: HLA-DPB1 Match

Donor ID	Comment on DP Matching	Total		UK&I		RoW	
		Number	%	Number	%	Number	%
1	DP Identical Match	36	92	14	100	22	88
	Permissive	4	10	0	0	4	16
2	DP Mismatch	27	69	12	86	15	60
	Perr						
	HvG						
	High						
3	DP M						
	Perr						
	HvG						
	Low						
4	DP I						
	Permissive	6	15	2	1		
5	DP Mismatch (x2)	27	69	11	7		
	Permissive	37	95	14	1		
	HvG Direction	1	3	0			
	GvH Direction	1	3	0			
	Bidirectional	2	5	1			
6	DP Mismatch (x2)	25	64	11	7		
	Non-permissive	37	95	14	1		
	HvG Direction	32	82	13	9		
	Bidirectional	1	3	0			

Donor Number and Registry	HLA-DQB1	HLA-DPB1
Patient	*03:01 06:02*	*04:01*
Donor 1 Germany	03:01 06:02	04:01
Donor 2 Germany	03:01 06:02	01:01 04:01
Donor 3 Austria	03:01 06:02	02:01 04:01
Donor 4 UK	03:01 06:02	04:01
Donor 5 UK	03:01 06:02	01:01 02:01
Donor 6	03:01	03:01

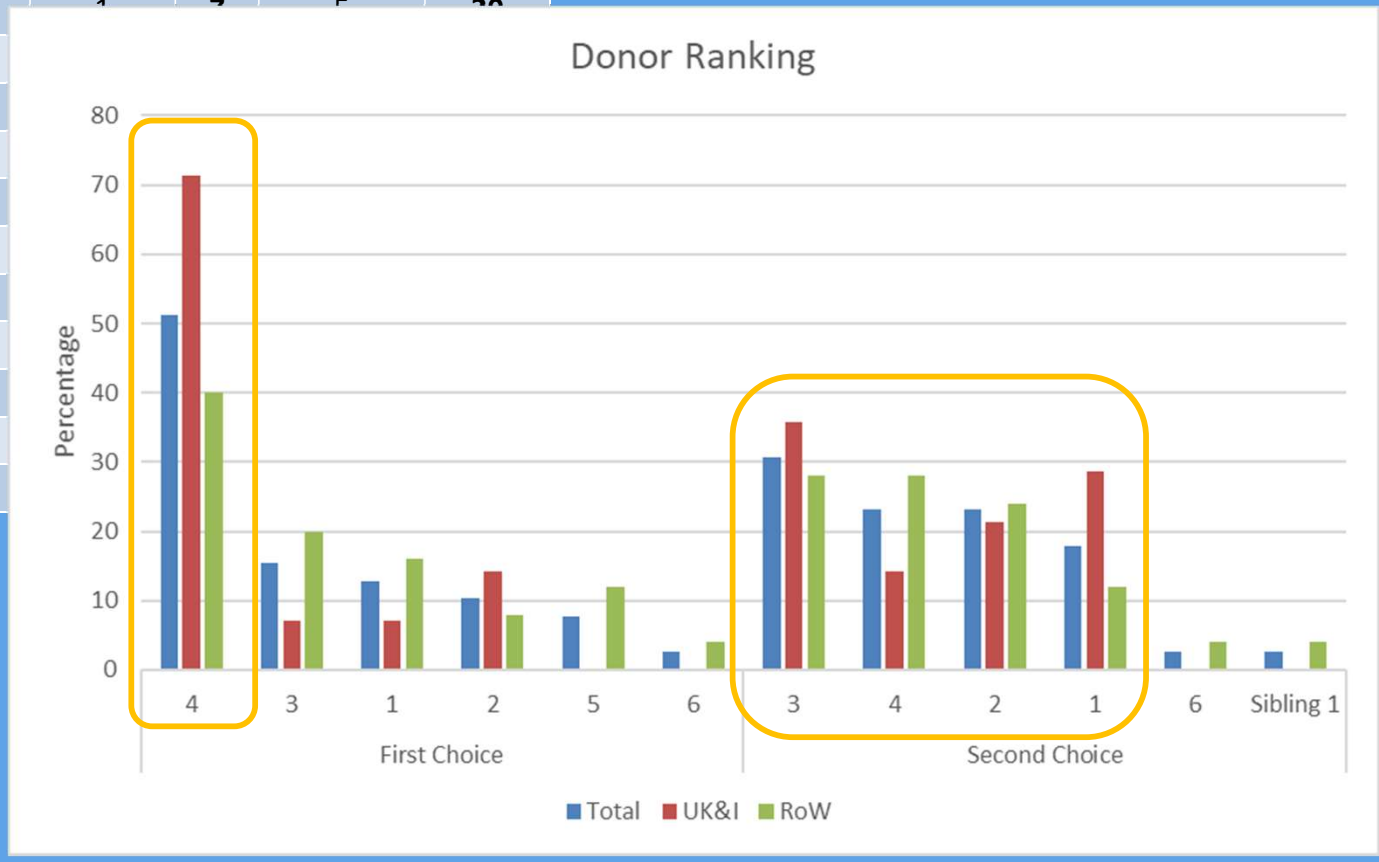
Comments:
Using the DP TCE Tool available at: https://www.ebi.ac.uk/ipd/imgt/hla/matching/
Donor 2 - Permissive
Donor 3 - Permissive
Donor 5 - Permissive
Donor 6 - Non-permissive HvG



Rank the top two preferred donors

Priority	Donor ID	Total		UK&I		RoW	
		Number	%	Number	%	Number	%
First Choice	4	20	51	10	71	10	40
	3	6	15	1	7	5	20
	1	5	13				
	2	4	10				
	5	3	8				
	6	1	3				
Second Choice	3	12	31				
	4	9	23				
	2	9	23				
	1	7	18				
	6	1	3				
	Sibling 1	1	3				

Donor Number and Registry	Sex	Age	Blood group	CMV	HLA-DPB1
Patient	*M*	*47*	*O+*	*Pos*	*04:01*
Donor 1 Germany	M	23	A+	neg	04:01
Donor 2 Germany	M	27	A+	pos	01:01 04:01
Donor 3 Austria	M	23	B+	pos	02:01 04:01
Donor 4 UK	F	23	O+	pos	04:01
Donor 5 UK	M	47	O+	pos	01:01 02:01
Donor 6 Germany	M	33	O+	pos	03:01 09:01



Reasons for Donor Selection

Donor ID	Reasons for Selection
Donor 1	
Donor 2	
Donor 3	
Donor 4	
Donor 5	
Donor 6	
Sibling 1	

Comments:
The strategy of selecting donors within this scenario will depend on how laboratories prioritise secondary characteristics such as DP match, ABO, CMV, age and gender.
The majority of participants selected Donor 4 (12/12 match, CMV and ABO match, young, female and from a reliable registry) as the first choice donor whilst the second choice donor was much more split. There is also the option of a haplo-identical sibling donor to consider. Interestingly, only one participant would select this sibling as a donor option.

Sibling 1 - Sister 49 years		
HLA-A	A*01:01	A*02:01
HLA-B	B*07:02	B*44:02
HLA-C	C*05:01	C*07:02

Sibling 2 - Brother 52 years		
HLA-A	A*01:01	A*02:01
HLA-B	B*08:01	B*44:02
HLA-C	C*05:01	C*07:01
RB1	DRB1*01:01	DRB1*04:01
QB1	DQB1*03:01	DQB1*05:01
PB1	DPB1*03:01	DPB1*04:01

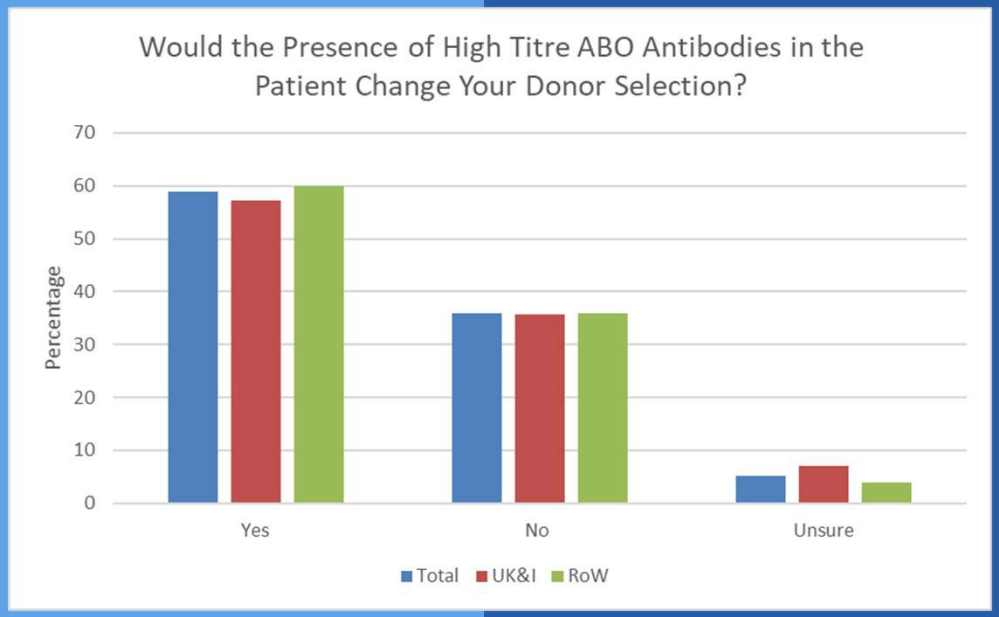
				ood oup	CMV	HLA-DPB1
					Pos	***04:01***
					neg	04:01
					pos	01:01 04:01
					pos	02:01 04:01
					pos	04:01
					pos	01:01 02:01
Donor 6 Germany	M	33	O+		pos	03:01 09:01

Further information

The clinical team inform you that the patient has high titre anti-A and anti-B antibodies:

Antibody	Titre End Point
Anti A	1 in 2048
Anti B	1 in 1024

Would this change your donor selection?



YES

59%

Unsure

5%

NO

36%

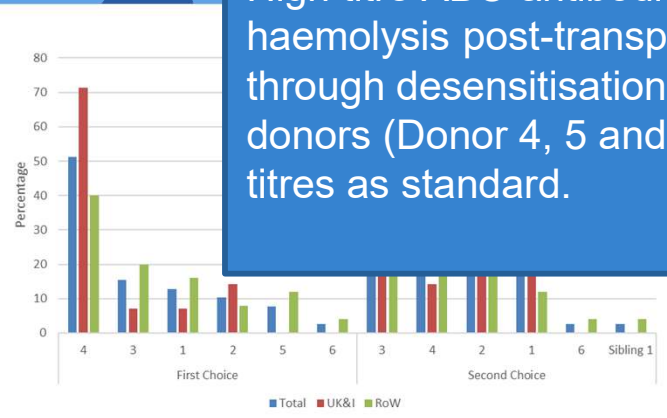
Revised donor choice

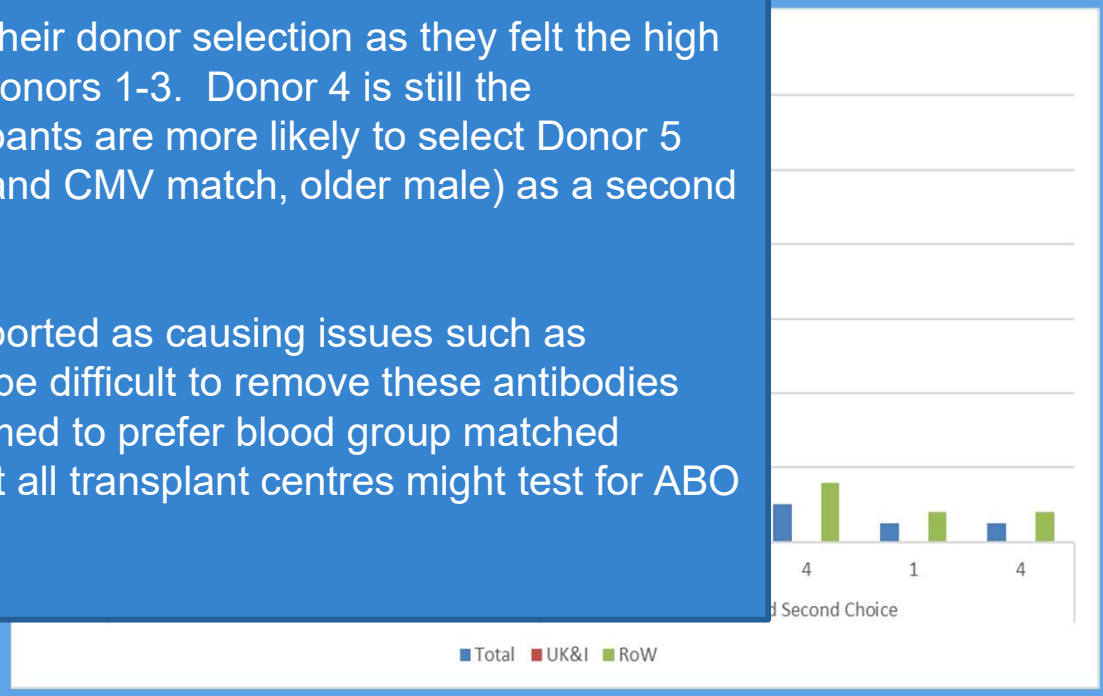
59% Changed Selection	Donor ID	Total		UK&I		RoW	
		Number	%	Number	%	Number	%
	4	19	**49**	8	**57**	11	**44**

Comments:

The majority of participants would alter their donor selection as they felt the high titre Anti-A and -B antibodies ruled out donors 1-3. Donor 4 is still the predominant first choice but now participants are more likely to select Donor 5 (10/12, permissive DP mismatch, ABO and CMV match, older male) as a second choice option.

High titre ABO antibodies have been reported as causing issues such as haemolysis post-transplant. It can also be difficult to remove these antibodies through desensitisation. Most labs seemed to prefer blood group matched donors (Donor 4, 5 and 6). However, not all transplant centres might test for ABO titres as standard.





Further information

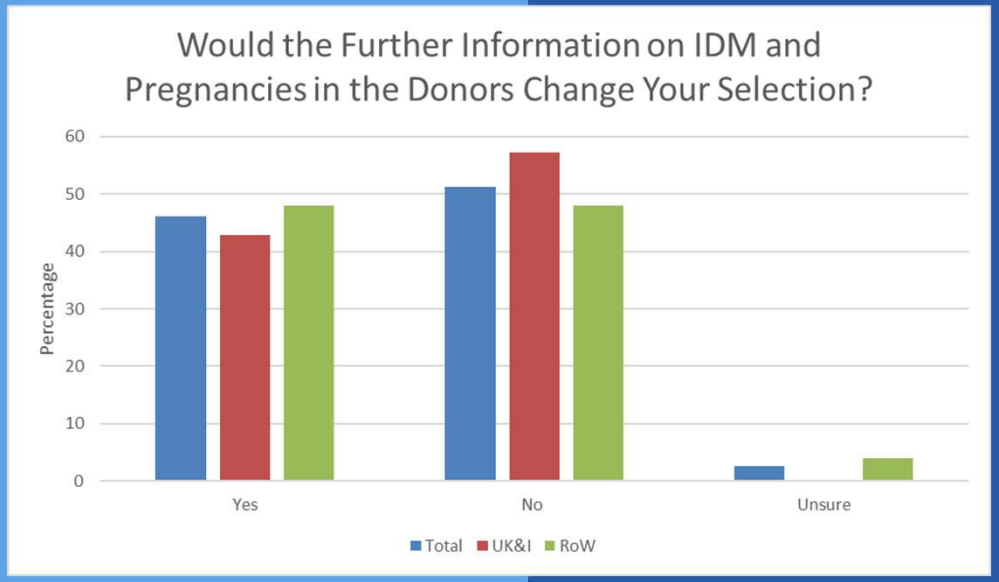
You are then given the results of further infectious disease marker testing for both the patient and the unrelated donors:

Patient KW: Blood group O+, CMV+, EBV+, HSV+

Donor Number and Registry	Sex	Age	Blood group	Cytomegalo-virus (CMV)	Hepatitis B Surface Antigen (HBsAg) Screen	Epstein-Barr Virus (EBV)	Human Immuno-deficiency Virus (HIV)	Herpes Simplex Virus (HSV)
Donor 1 Germany	M	23	A+	negative	negative	positive	negative	positive
Donor 2 Germany	M	27	A+	positive	negative	negative	negative	positive
Donor 3 Austria	M	23	B+	positive	negative	positive	negative	positive
Donor 4 UK	F	23	O+	positive	negative	positive	negative	negative
Donor 5 UK	M	47	O+	positive	negative	positive	negative	positive
Donor 6 Germany	M	33	O+	positive	negative	positive	negative	positive

You are also told that Donor 4 has had two pregnancies.

Would this change your donor selection?



YES

46%

Unsure

3%

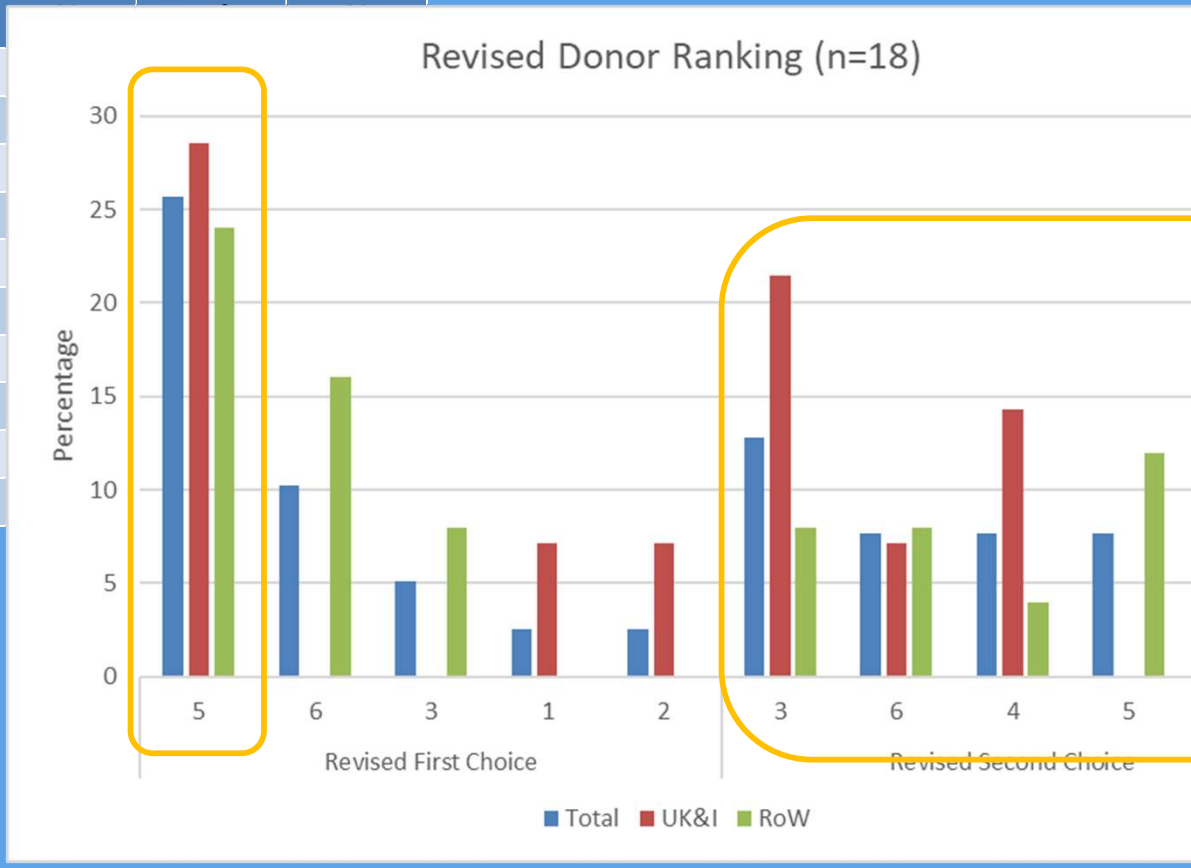
NO

51%

Revised donor choice after IDM results

46% Changed Selection	Donor ID	Total		UK&I	RoW
		Number	%	Number	
Revised First Choice	5	10	26	4	
	6	4	10	0	
	3	2	5	0	
	1	1	3	1	
	2	1	3	1	
Revised Second Choice	3	5	13	3	
	6	3	8	1	
	4	3	8	2	
	5	3	8	0	
	2	3	8	0	

Donor Number and Registry	Sex	Age	Blood group	Cytomegalo-virus (CMV)	Epstein-Barr Virus (EBV)	Herpes Simplex Virus (HSV)
Patient	M	47	O+	Positive	Positive	Positive
Donor 1 Germany	M	23	A+	negative	positive	positive
Donor 2 Germany	M	27	A+	positive	negative	positive
Donor 3 Austria	M	23	B+	positive	positive	positive
Donor 4 UK	F	23	O+	positive	positive	negative
Donor 5 UK	M	47	O+	positive	positive	positive
Donor 6 Germany	M	33	O+	positive	positive	positive



Reasons for Revised Donor Selection													
Donor ID	12/12 Match	11/12 Match	10/12 Match	Permissive DP	Non-Permissive DP (HvG)	ABO Match	CMV Match	Young	Male	EBV Matched	HSV Matched	Titre Anti-A Antibodies	Comments
Donor 1	✓							✓	✓				Donors 1-4 now excluded due to high titre anti-A/B antibodies or virology results
Donor 2		✓											
Donor 3		✓											
Donor 4	✓												Two previous pregnancies.
Donor 5			✓	✓		✓				✓	✓		
Donor 6			✓		✓	✓	✓			✓	✓		

Comments

After the inclusion of further information regarding testing for infectious diseases and some information regarding pregnancies for Donor 4 a split decision was noted regarding whether participants would change their donor selection. Those that would alter their donor selection favoured Donor 5 as first choice but again, decisions on second choice were split. Many participants commented that donors 1-4 were now excluded due to high titre anti-A/B antibodies, virology results (and the associated risk of post-transplant lymphoproliferative disease (PTLD)) or prior pregnancies (and increased risk of GvHD). Donor 5 offers a 10/12 permissable DP match older donor which participants generally favoured over Donor 6 which was younger but had a non-permissive DP mismatch.

	Epstein-Barr Virus (EBV)	Herpes Simplex Virus (HSV)
	Positive	Positive
	positive	positive
	negative	positive
	positive	positive
	positive	negative
	positive	positive
	positive	positive

Further information

Patient KM was transplanted with an unrelated donor on 22/03/2021. Post-transplant the patient has had some problems with persistent infections which have required readmission.

The lab has been receiving regular samples for chimerism testing. The results of peripheral blood percentage donor chimerism are shown in the table below:

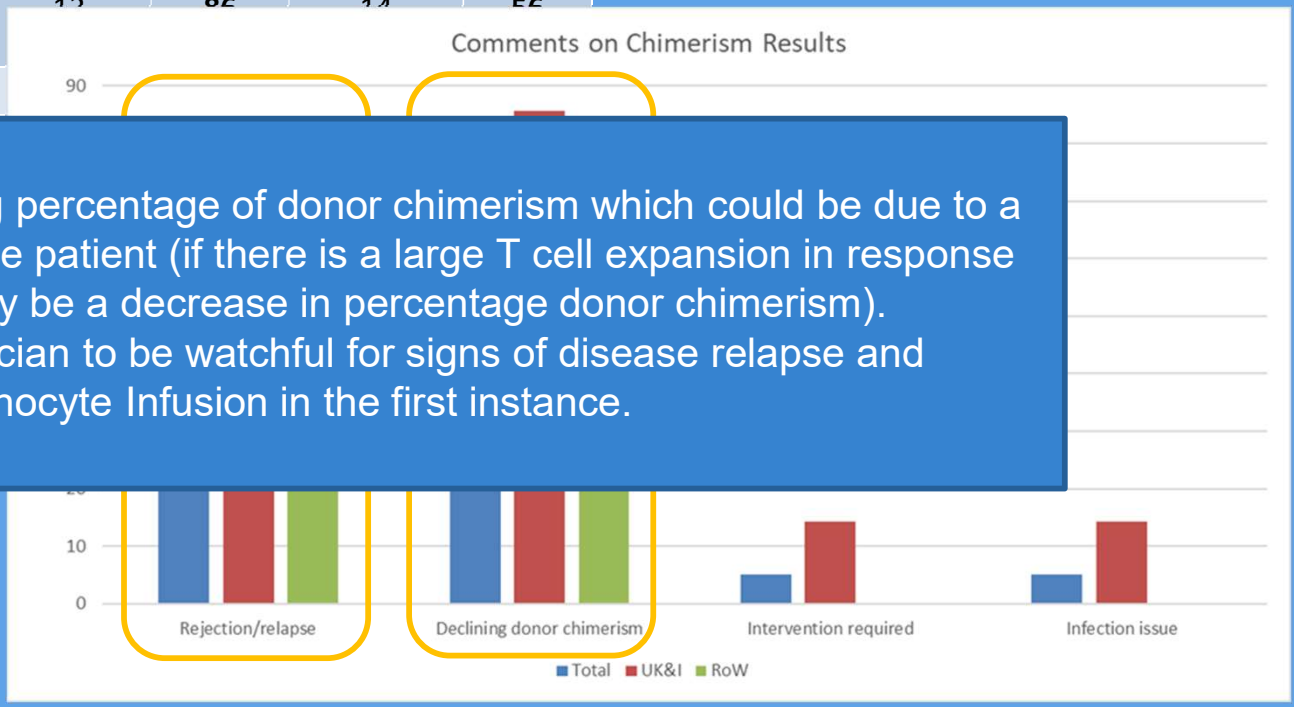
Date Taken	Whole Blood	T Cells	Myeloid	B cells
21/04/2021	92%	79%	96%	90%
04/05/2021	98%	NT*	NT*	NT*
10/05/2021	94%	79%	94%	99%
06/06/2021	63%	62%	70%	94%
04/07/2021	35%	52%	40%	74%

**Not tested – insufficient cells*

Q3: Comment on Chimerism Results

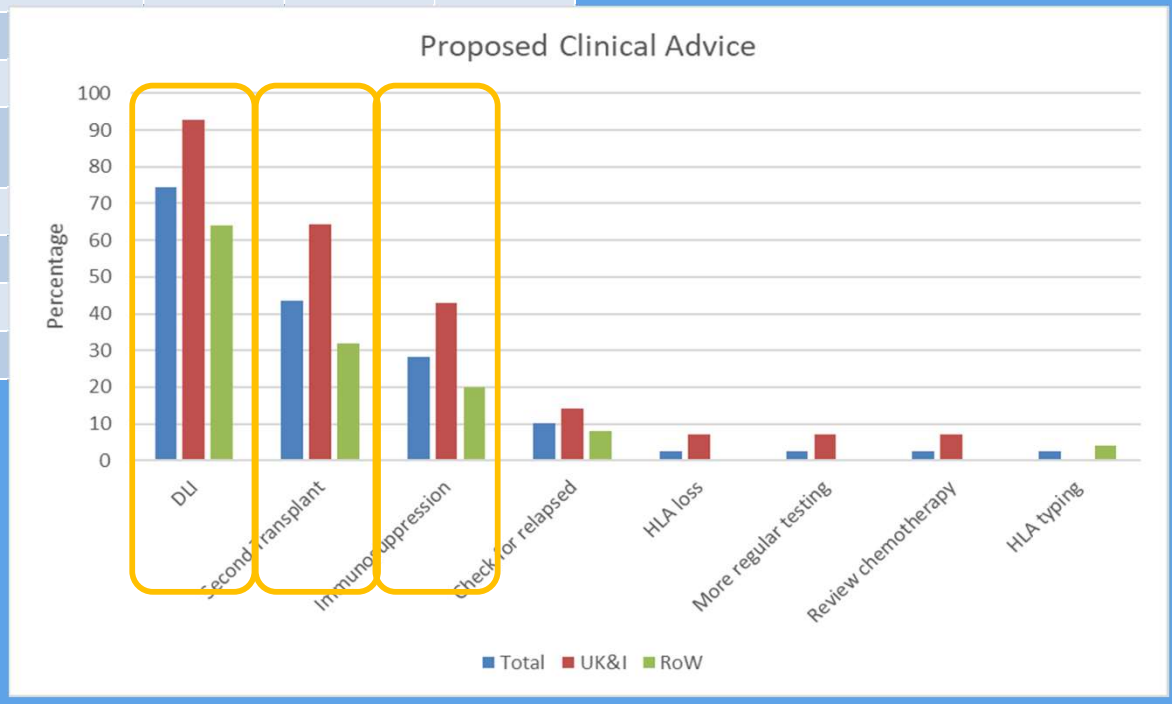
Comment on Chimerism Testing	Total		UK&I		RoW	
	Number	%	Number	%	Number	%
Rejection/relapse	27	**69**	11	**79**	16	**64**
Declining donor chimerism	26	**67**	12	**86**	14	**56**
Intervention required	2	**5**				
Infection issue						

Comments:
The patient has a falling percentage of donor chimerism which could be due to a persistent infection in the patient (if there is a large T cell expansion in response to an infection there may be a decrease in percentage donor chimerism).
We would advise a clinician to be watchful for signs of disease relapse and consider a Donor Lymphocyte Infusion in the first instance.



What clinical advice would you offer?

Clinical Advice	Total		UK&I		RoW	
	Number	%	Number	%	Number	%
Donor Lymphocyte Infusion	29	**74**	13	**93**	16	**64**
Second Transplant	17	**44**				
Decrease Immunosuppression	11	**28**				
Check if MDS has relapsed or transformed	4	**10**				
HLA loss	1	**3**				
More regular testing	1	**3**				
Review chemotherapy	1	**3**				
Perform verification HLA typing	1	**3**				



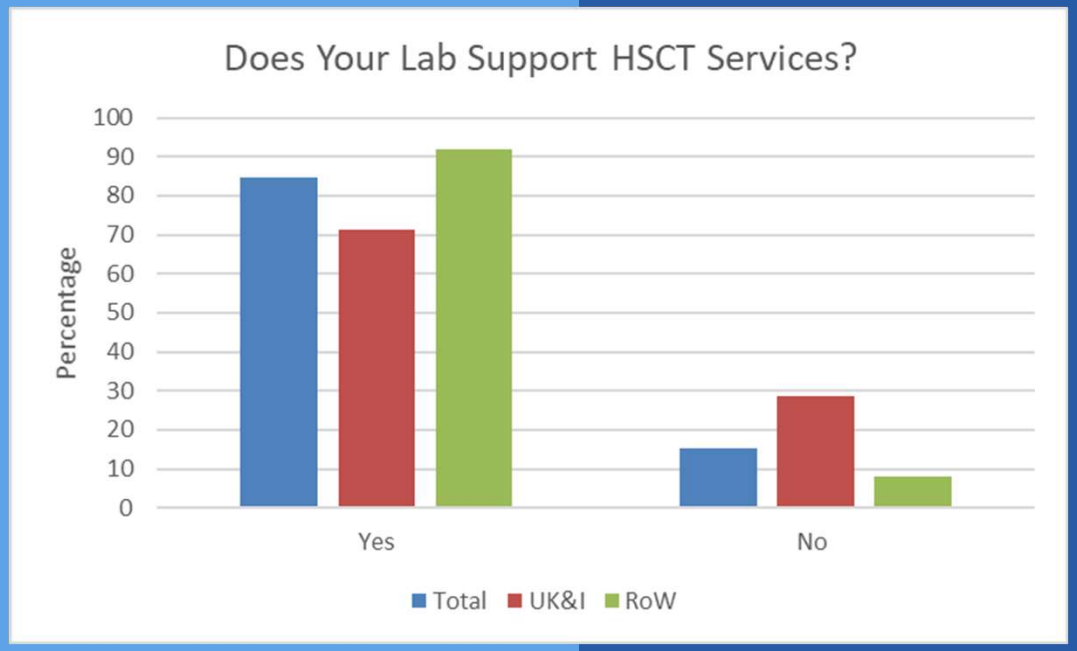
Q8: Does your lab provide a clinical HSCT service?

YES

85%

NO

15%



Further Comments

- Thought provoking scenario creating some good discussion about donor selection.
- Patient weight – it will help in donor selection to include or exclude potential female donors. Patient HLA antibody profile – it will help in do… selection in case of selecting HLA mismatched donor.
- In a real life situation additional information - such as accredited registry status, weight/size of donors, availability of donors, HLA Abs/potential DSA in recipient - would be available and useful.
- It would have been useful to know the stem cell source to be used for transplant as this would increase or decrease the importance of ABO matching. Major ABO incompatibility is not a contraindication for HSCT at our local Transplant Centre, even in the presence of high titres.
- We would not automatically have access to anti-A and anti-B Ab titre information for HPCT donor selection in this lab, although we consider blood group matching and avoiding major ABO mismatch where possible as per the BSHI guidelines for HPCT donor selection.
- Does the clinical urgency of the case permit the reduction of the titer of incompatible recipient isoheamagglutinins? Monitor ABO antibody titre post graft.
- It is interesting to see the selection of IDMs highlighted in the current IED. It would be interesting to note how many labs would use all these IDM results in the selection of the optimal unrelated donor option. Priority is given to donors who are CMV matched over DPB1 match or permissive mismatch. Young males donors also preferred. Donor selection is often completed before an extended virology report is received. Transplant Centre would not change donor choice based on this information. The only exception is for patients where EBV is relevant to the primary disease.
- As a lab, we follow BSHI guidelines for HLA matching and donor selection of HPCT, with no reference to virology for selection other than CMV. We excluded the CMV negative donor (donor 1) on this basis. We are aware of the risk of EBV related PTLD post HPCT and that the risk of EBV-PTLD is related to the degree of T cell depletion and selection of suitable donors but this is not routine practice in our laboratory and is a clinical decision.
- Our approach is constantly evolving. For example, due to experience of post-transplant complications attributed to infectious disease, our strategy is becoming increasingly focused on matching according to virology in addition to HLA and other factor.

Further Comments

- Good Scenario. Some elements of the patient's treatment, which may impact donor selection, would be within the remit of the clinical team rather than H&I lab, e.g. donor/recipient virological mismatching for HSV.
- Many of these decisions would be made through discussions with our Transplant Centres as they have preferences with regards to the level of risk they are willing to take in relation to ABO mismatching, HSV/EBV mismatching and use of multiparous donors.
- The limitations of our laboratory are that we are not directly involved in managing the patients and cannot monitor the other laboratory investigations which are performed at their respective hospitals.
- The advent of new therapeutics against CMV has recently changed the criteria of donor choice : is the CMV compatibility still more important than ABO group ? Is the DP compatibility more important than CMV and ABO group ? The proportion of each criteria during the donor choice procedure is still not clear and vary from one center to another.
- ABO incompatibility does not seem to have great weight for most of the transplant centers we work with, CMV is the larger problem as many treatments lead to fragile grafts.
- The sibling haplo-identical donors were not considered in the top ranking donors as our centre will not consider these if a 12/12 or 10/10 DP permissive unrelated donor is available for both adult and paediatric patients.
- Our Laboratory does not perform chimerism testing or interpretation.
- More information is needed regarding the HLA matching of the donor and recipient and infectious markers.

Summary

Donor ID	Matching Criteria										
	12/12 Match	10/12 Match	Permissive DP	ABO Identical	<35 years	Male	Previous Pregnancies	CMV Match	EBV Matched	HSV Matched	Anti-ABO Antibodies Present
Donor 1	✓				✓	✓			✓	✓	✓
Donor 2			✓		✓	✓		✓		✓	✓
Donor 3			✓		✓	✓		✓	✓	✓	✓
Donor 4	✓			✓	✓		✓	✓	✓		
Donor 5		✓	✓	✓		✓		✓	✓	✓	
Donor 6		✓		✓	✓	✓		✓	✓	✓	

Thanks!

Do you have any questions?

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