REDUCING DECEASED DONOR KIDNEY COLD ISCHAEMIC TIMES BY MODIFYING CROSS MATCH PRACTICES

Introduction and clinical case

A transplant unit accepted a kidney from a donation after brain death donor aged in their late 40s in June 2018. Twelve hours later (1146) the donor was cross-clamped, and the organ was retrieved and transported 100 miles away to the implanting centre. At 2311 the Hub was notified that the cross match was positive, and the organ was offered on. The unit has a policy of using donor peripheral blood lymphocytes (PBLs) for cross matches (XM) for 'local' donors, but has concerns about the costs of transporting PBLs from donors further afield.

The kidney was then declined for a paediatric patient due to prolonged cold ischaemic time (CIT) at 2339. It entered the Kidney Fast Track Scheme at 0039 the next day and was declined by three other units due to prolonged CIT. It was eventually accepted and implanted by a fourth centre.

This case was identified through the Declined Kidney Offer Scrutiny Scheme, and prompted a discussion between Chris Callaghan, Sue Fuggle, Tracey Rees, Andrea Harmer (Chair of the British Society for Histocompatibility and Immunogenetics (BSHI)), and other colleagues.

At present there is no specific national guidance regarding which XM techniques should be used, despite the organ utilisation implications of prolonged organ CITs if an unexpected positive XM occurs. More commonly, waiting for a XM from donor spleen / lymph nodes prolongs organ CITs even if the result is negative, as the transplant cannot proceed until the result is received.

KAG is asked to consider if specific national guidance is required in this area, and, if so, how best to take these issues forward.

Background

HLA typing and cross matching are essential components of successful living and deceased donor kidney transplant programmes. Histocompatibility and immunogenetics (H&I) laboratories in the UK have developed varying approaches to avoid the

transplantation of deceased donor kidneys into recipients with significant titres of anti-donor antibodies. Two broad approaches are used, i.e.:
1) incubation of the potential recipient's serum with a source of donor lymphocytes bearing both HLA class I and II molecules (cross match – XM).
2) knowledge of the potential recipient's anti-HLA antibody profile and the donor's tissue type enables a 'virtual cross match' (VXM) to be performed, i.e. a risk assessment of the likelihood of a positive cross match if an 'actual' cross match was to be performed.

Donor lymphocytes can be separated from donor tissue after organ retrieval (e.g. spleen or lymph node) or prior to organ retrieval (e.g. donor PBLs). The VXM can be based on historic samples, or on a sample taken from the potential recipient at the time of admission for a transplant. All live donor kidney transplants require PBL XMs.

The advantage of the PBL XM and the VXM is that they can be performed prior to organ retrieval, thus minimising organ CIT. The disadvantages of the PBL XM are that donor blood is required and extra transport costs are incurred. The VXM relies on accurate donor HLA typing and recipient antibody characterisation.

National survey

A survey of all 21 UK H&I laboratories linked to kidney transplant units was performed in October 2018 by the BSHI. A Survey Monkey link was sent to all heads of laboratories. The questions covered the use of 'wet' cross matches using spleen / LNs and PBLs, as well as the use of VXM and HLA antibody testing in the on-call setting. Seventeen laboratories responded (response rate 81%).

The results were as follows (see also Appendix 1):

- For deceased donor kidney transplantation, 5/17 laboratories routinely use PBL XM (29.4%); 1/17 laboratory never uses PBL XM (5.88%). All laboratories perform S/LN cross matches as required (routinely or sometimes).
- All laboratories obtained cross match results within 6 hours, whether using S/LN or PBL. The question that was not asked which may have been relevant to donor cell source is whether the cross match result was available before the organ was shipped to the transplant unit. Most units take 4-6 hours to perform a XM.
- A trend to performing PBL XM for local donors was visible (11/17 laboratories – 64.71%), though 7/11 laboratories (41.18%) also performed PBL XM for imported donors. Comments indicated that the use of PBL XM was considered on a case-by-case basis, depending on the clinical urgency or following discussion with the clinical team.
- Regarding barriers to or concerns with using PBL XM, the following themes were visible in the response:

    - 13/17 laboratories (76.47%) commented on either the quality or number of cells obtained from peripheral blood and assay concerns. However, it must noted here that respondents were asked to tick all answers that applied, so it is not possible to definitively state that these answers were from 13 individual laboratories or if some respondents ticked several similar answers.
    - 4/17 laboratories (23.53%) mentioned the cost of transporting samples as a reason why PBL XM are not performed.
- Only one laboratory was unaware PBLs can be requested for all donors. One laboratory proceeded to transplant in 85% cases on the basis of a VXM, so there has been no need to implement PBL XM.
- 13/17 laboratories (76.47%) routinely perform VXM for unsensitised patients. All laboratories perform VXM to some extent for unsensitised patients.
- 3/17 (17.65%) laboratories never perform VXM for sensitised patients.
- 11/17 laboratories (64.71%) perform HLA antibody testing on fresh samples out of hours in support of VXM if required.

Other considerations

Prolonged organ CIT increases the likelihood of kidney delayed graft function (DGF), and, in some cases, will decrease graft survival. DGF requires post-transplant dialysis and often results in a prolonged inpatient stay. An approximate tariff for one session of inpatient dialysis is £150; the tariff for a 24-hour inpatient stay is £215 (Guy's Hospital data). The cost of transporting donor PBLs 100 miles is £210 (Amvale data).

The VXM and donor PBL approaches have been shown to significantly reduce deceased donor kidney CITs in the UK (Taylor CJ et al, *Transplantation* 2010; Shrestha S et al, *Transplantation* 2016).

There are anecdotal reports that SNODs can occasionally be unwilling to take donor PBL samples. Anthony Clarkson has been emailed and he sees no significant barriers to the use of donor PBLs for XM. In the experience of one of the authors, there has never been any concern raised by a single SNOD despite the routine requesting of donor PBLs in the last 5-6 years (CC).

Summary

1) H&I techniques play an important role in facilitating the reduction of deceased donor kidney CITs. There is no specific national guidance for clinicians or H&I laboratories in this area.

2) H&I laboratories appear able and willing to perform XM using donor PBLs, or using VXM techniques, but organisational and financial concerns from clinicians may limit the use of PBL XMs.

3) A co-ordinated national approach is likely to reduce organ CITs, and may occasionally prevent organ discard.

4) The views on the above are sought from KAG.

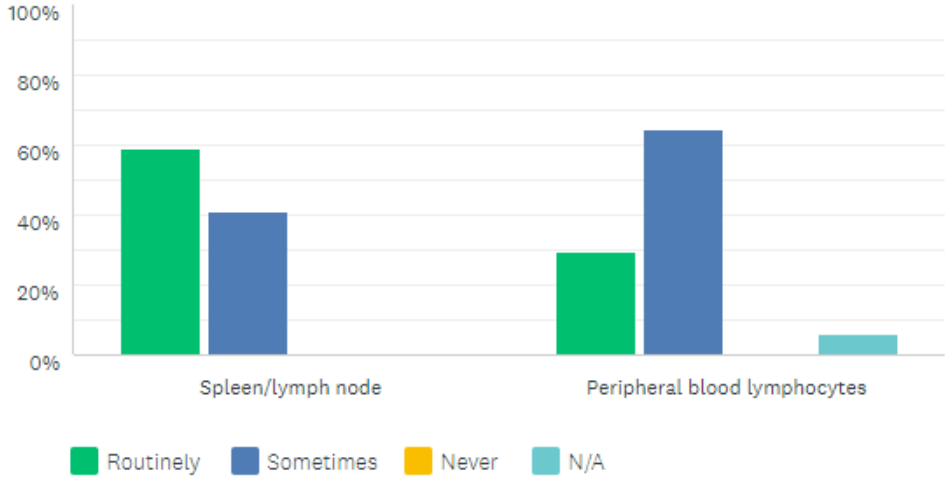
Chris Callaghan, Tracey Rees, Natalia Diaz Burlinson, Andrea Harmer, Sue Fuggle

Appendix 1 – survey graphs and free text

Q2

For deceased donor transplantation do you perform wet crossmatches with:

Answered: 17 Skipped: 0

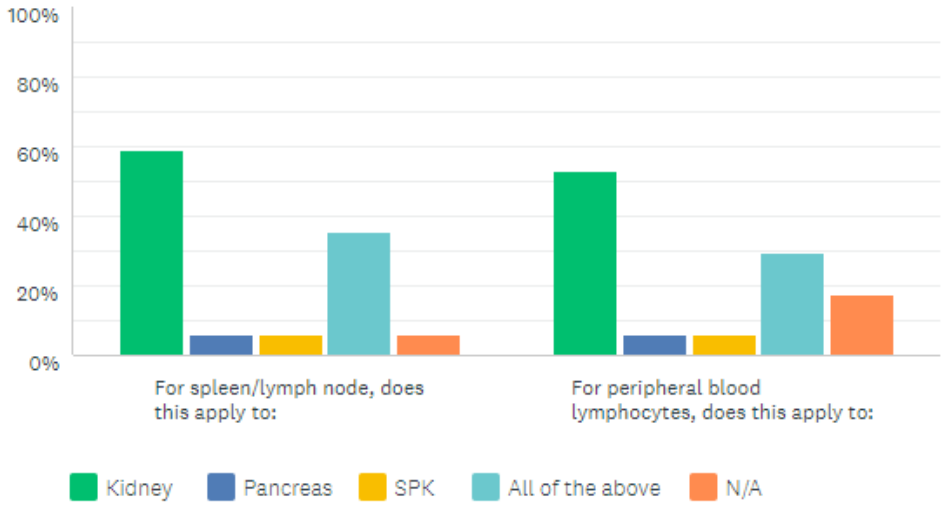


	ROUTINELY	SOMETIMES	NEVER	N/A	TOTAL RESPONDENTS
Spleen/lymph node	58.82% 10	41.18% 7	0.00% 0	0.00% 0	17
Peripheral blood lymphocytes	29.41% 5	64.71% 11	0.00% 0	5.88% 1	17

Q3

For the wet crossmatches performed:

Answered: 17 Skipped: 0

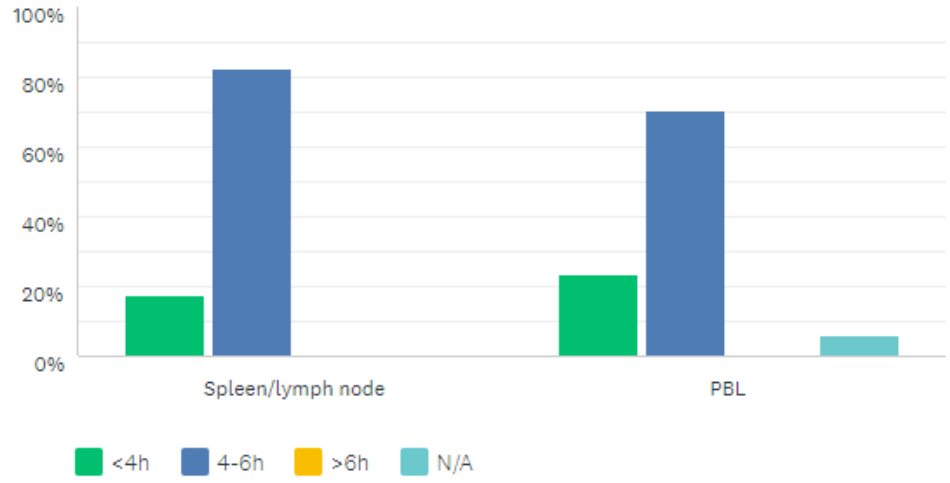


	KIDNEY	PANCREAS	SPK	ALL OF THE ABOVE	N/A	TOTAL RESPONDENTS
For spleen/lymph node, does this apply to:	58.82% 10	5.88% 1	5.88% 1	35.29% 6	5.88% 1	17
For peripheral blood lymphocytes, does this apply to:	52.94% 9	5.88% 1	5.88% 1	29.41% 5	17.65% 3	17

Q4

What is the average time to perform a crossmatch for:

Answered: 17 Skipped: 0

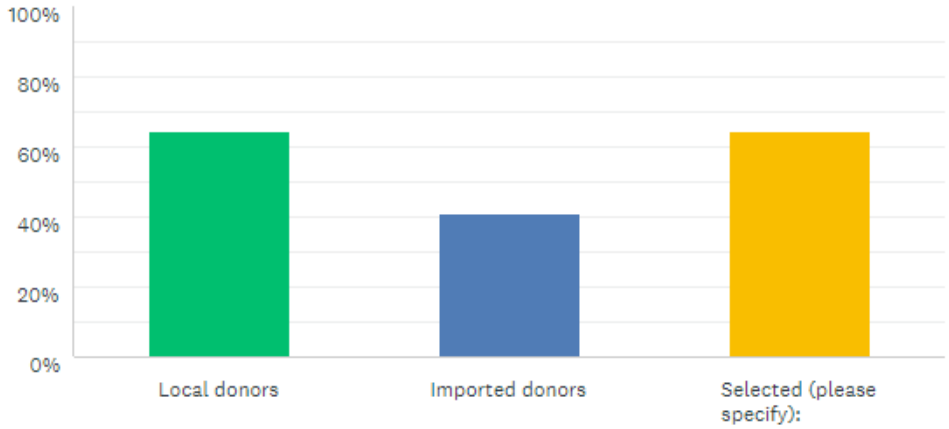


	<4H	4-6H	>6H	N/A	TOTAL
Spleen/lymph node	17.65% 3	82.35% 14	0.00% 0	0.00% 0	17
PBL	23.53% 4	70.59% 12	0.00% 0	5.88% 1	17

Q5

Where PBL crossmatches are performed, are these for:

Answered: 17 Skipped: 0



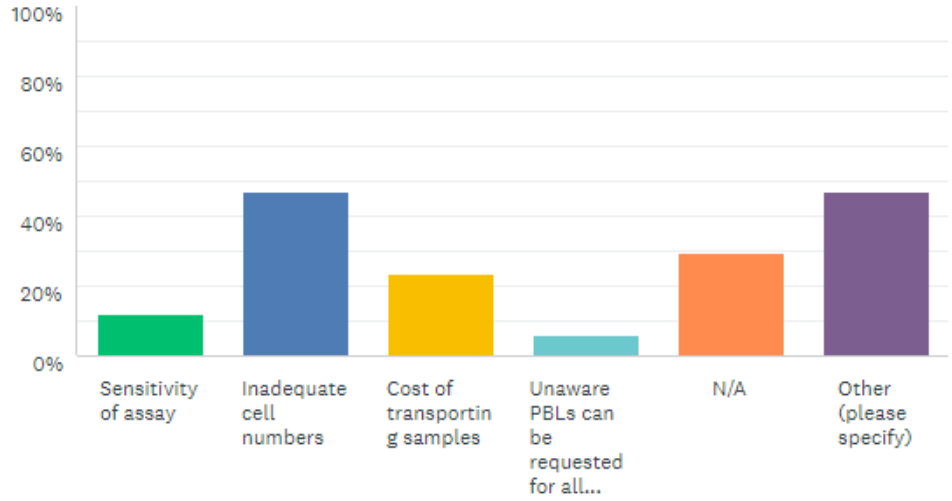
ANSWER CHOICES		RESPONSES	
Local donors		64.71%	11
Imported donors		41.18%	7
Selected (please specify):	Responses	64.71%	11
Total Respondents: 17			

- Usually local donors when we have peripheral blood. Although we have also been able to get peripheral blood from donors being typed in Edinburgh and some other places.
- Routinely performed for local. Performed for selected imported for sensitised patients and at surgeon's request
- All wet crossmatch unless PB not sent (rare).
- DCD mainly
- Less often for imported donors
- PBL XM utilised for hand-transplant recipients only
- It can be both local and imported donors and results from a discussion with the transplant unit and the expected benefit on CIT of undertaking a crossmatch on PBLs versus spleen. Sensitisation status of the potential recipient is also a factor as the crossmatch may require FCXM plus CDC or several serum samples if there are complex potential DSAs
- If requested by transplant coordinators and need for urgency
- if a crossmatch is deemed to be necessary and things can be expedited by getting hold of peripheral blood samples then we would endeavour to do this. Mostly this would be when we have a local donor, but we have requested extra samples from donors to try and get the crossmatch started before tissues arrive.
- We use PBL crossmatches only in the Living Donor Programme
- Occassionally asked to perform wet XM pre retreval or for patients with splenectomy

Q6

What reasons apply for not performing PBL crossmatches (please tick all that apply):

Answered: 17 Skipped: 0



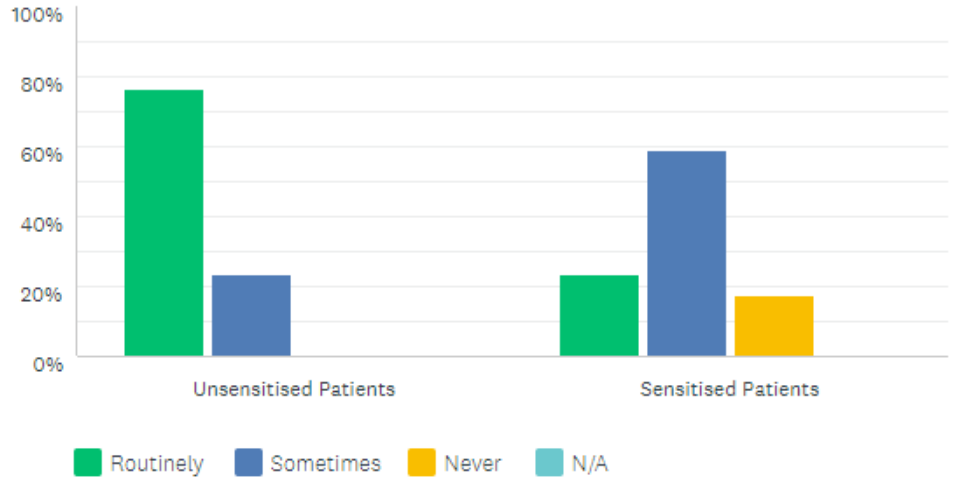
ANSWER CHOICES		RESPONSES	
Sensitivity of assay		11.76%	2
Inadequate cell numbers		47.06%	8
Cost of transporting samples		23.53%	4
Unaware PBLs can be requested for all donors		5.88%	1
N/A		29.41%	5
Other (please specify)	Responses	47.06%	8
Total Respondents: 17			

- Viability and lymphocyte purity can be poor for PBL
- Some concern over quality of donor B-cells particularly when used for patients with HLA class II reactive antibodies - however I think this is more of a historic concern as we haven't had any issues recently. I was not aware that we could request PBLs for all donors ! and have only done this when the donor has been reasonably near!
- If retrieval has already commenced at the time of offer
- 85% of our transplants go ahead with a virtual XM. The decision not to use PBL was taken before I became Lab Director and because of our Virtual XM policy we haven't needed to revisit it. However, it is something I would be prepared to try again if it was an option and widely available because it works well enough for the Living Donor programme. We only crossmatch the most immunologically challenging patients and we would need to check that our Living Donor XM protocol is sensitive enough.
- Variable 'Quality' of lymphocytes obtained
- Spleen comes with organ and gives enough material for full crossmatches
- If the organs are being transported by air, it may be decided that the cost of an earlier flight with bloods is not justified.
- Occasionally we can't use PBL as the organs have already been retrieved, so blood can no longer be provided. We will use PBL wherever possible otherwise.

Q7

Are virtual crossmatches performed for:

Answered: 17 Skipped: 0

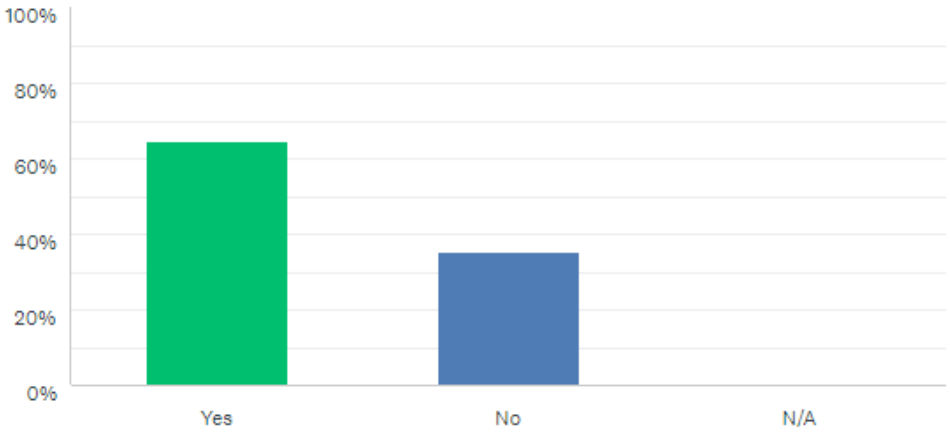


	ROUTINELY	SOMETIMES	NEVER	N/A	TOTAL
Unsensitised Patients	76.47% 13	23.53% 4	0.00% 0	0.00% 0	17
Sensitised Patients	23.53% 4	58.82% 10	17.65% 3	0.00% 0	17

Q8

Is antibody testing on fresh samples available 24/7 to support VXM if required:

Answered: 17 Skipped: 0



ANSWER CHOICES	RESPONSES	
Yes	64.71%	11
No	35.29%	6
N/A	0.00%	0
TOTAL		17

Q9

What proportion (%) of deceased donor crossmatches proceed on the basis of:

Answered: 17 Skipped: 0

ANSWER CHOICES		RESPONSES	
Spleen/lymph node XM	Responses	100.00%	17
PBL XM	Responses	88.24%	15
VXM	Responses	88.24%	15
N/A	Responses	5.88%	1

Lab	S/LN	PBL	XM

1	20	40	40
2	59	1	40
3	10%	5%	85%
4	When PBL not available	Almost all sensitised patients (unless PBL not available)	All unsensitised patients meeting criteria
5	38	38	24
6	57%	10%	33%
7	54	46	47
8	45	3	52
9	5%	1%	94%
10	16%	0%	84%
11	75	10	15
12	20	80	15
13	3	-	97
14	70	30	-
15	Information to follow		
16	5	60	35
17	8	12	80

Spleen/LN

Carried out when PBL not available or not enough cells.
Information to follow

PBL

almost all sensitized patients unless PBL not available

VXM

on all unsensitized patients meeting the local policy for VxM

approximate values