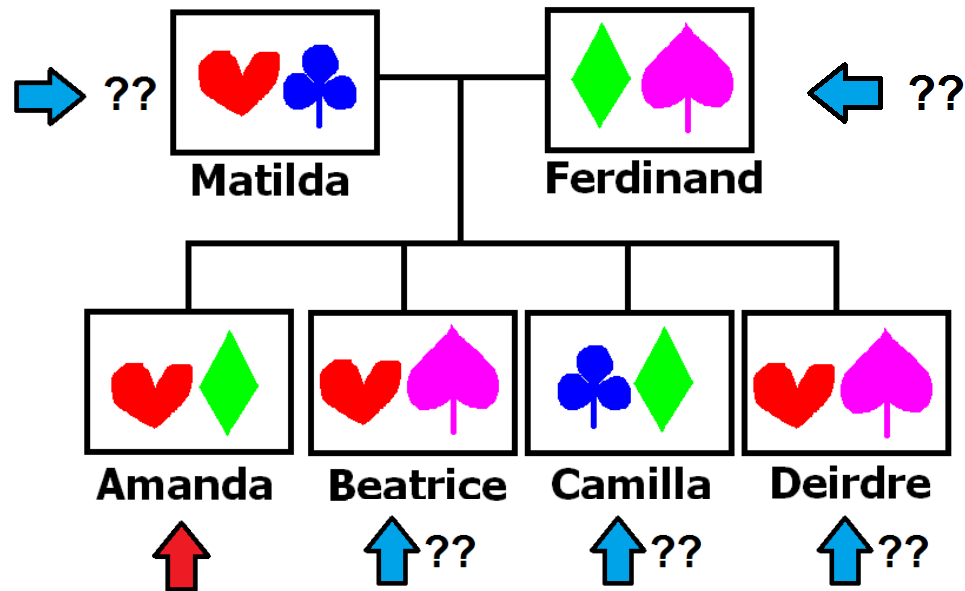


Haploidentical HPC transplant – the potential impact on an apheresis service



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HPC transplant – a reminder of the basics

- In the last few decades, it has been possible to treat a variety of diseases of the bone marrow (leukaemias, lymphomas, etc. but also non-malignant diseases like sickle cell disease) by transplantation of blood stem cells.
- There are three ways of getting hold of blood stem cells for transplantation:
 - **Either** physically suck **bone marrow** out of the donor's pelvis under general anaesthetic
 - **Or** collect peripheral blood stem cells (**PBSC**) by apheresis, using a cell separator machine
 - **Or** harvest umbilical cord blood, from the placenta and umbilical cord of a newborn baby, once the cord has been cut
- For adult donors, obviously only the first two methods apply
- The donor may either be **a close relative of the patient** who has the same or similar tissue type, or may be **an unrelated donor** – either an **adult registry donor** e.g. Anthony Nolan in the UK, or a **cord unit** from an umbilical cord bank

What is a haploidentical HPC transplant anyway?

- Haploidentical (“haplo”) HPC transplant is a radically new approach to HPC transplantation
- Unlike conventional HPC transplant, which uses a donor with the same or a very similar tissue type as the patient, haplo transplant uses a donor who is a close relative of the patient, but who shares only **half** of their tissue type genes
- “Haplo-” is a Greek root meaning “half”
- Two main approaches – the most widely used one is **post-transplant cyclophosphamide**
- To avoid the very severe (and possibly fatal) Graft-v-Host Disease that would usually result from this severe a tissue type mismatch, the recipient usually gets RIC conditioning, then receives a dose of a chemo drug, **cyclophosphamide**, 48 to 72 hours post-transplant
- The cyclophosphamide kills the “bad” alloreactive lymphocyte clones that would cause GvHD, because they are already proliferating rapidly in response to the antigenic challenge from the recipient’s unmatched tissue type proteins, but doesn’t affect the “good” lymphocyte clones that *aren’t* proliferating
- Patients are commonly quite sick with “Cytokine Release Syndrome” (basically hyperacute GvHD) for the initial 48 to 72 hours before the cyclophosphamide: often require HDU-level support

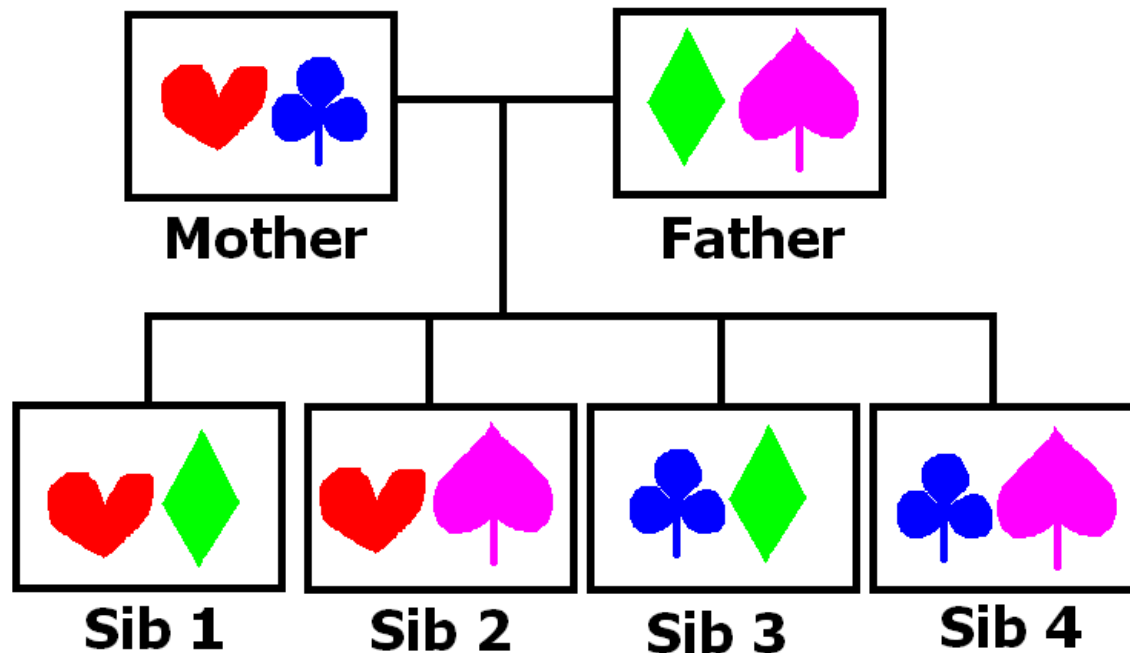
What is a haploidentical HPC transplant anyway?

- continued

- As an alternative to post-transplant cyclophosphamide, it is also possible to **T-cell-deplete** the PBSC product **after** collection (generally used in combination with **myeloablative** conditioning for children or younger adults)
- The big advantage of haplo transplant, by either method, is that it dramatically increases the available “pool” of related donors available for an individual patient** – very useful for patients with poor VUD or umbilical cord donor options
- Other than the initial Cytokine Release Syndrome, the RIC haplo approach with post-transplant cyclophosphamide is usually a surprisingly “gentle” transplant – severe GvHD is rare, and immunosuppression can usually be weaned early – good for older patients who are borderline allograft candidates

How tissue type genes and proteins are inherited

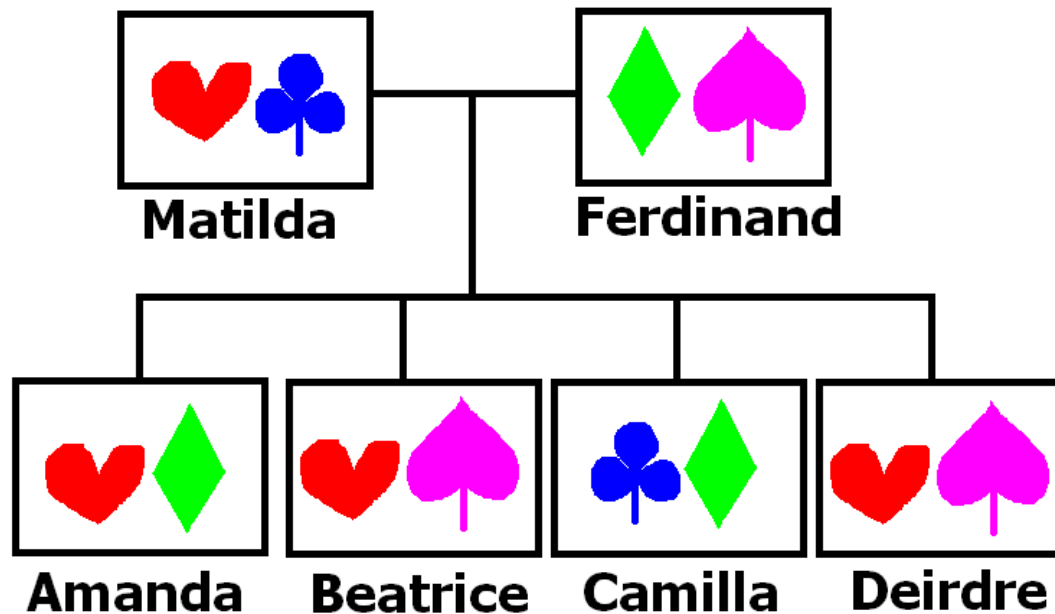
The tissue type (“HLA”) genes are clustered very close together on Chromosome 6. Tissue type genes (and therefore tissue type proteins) are inherited as “blocks” called haplotypes - one from mum and one from dad.



This means that full siblings have four possibilities for their tissue type, as shown above. The chance of each sib being a match for another specific sib is therefore 1 in 4, or 25%.

How tissue type genes are inherited - continued

However, inheritance of tissue types is random, like flipping a coin, and not all possibilities will necessarily occur in any given family.



In this family with four daughters, Beatrice and Deirdre are a full tissue-type match. However, Amanda and Camilla have no matched sibling available.

Don't try to remember the following: it's just an interesting factoid!!

**Chance of a tissue-type
matched sibling donor**

$$= 1 - \left(\frac{3}{4}\right)^n$$

**where n = number
of siblings**

The chances of a **fully** tissue-type-matched sibling donor being available for conventional HPC transplant are therefore:

- 25% with one sibling (i.e. family of two)
- 43.7% with two siblings (i.e. family of three)
- 57.8% with three siblings (i.e. family of four)
- ...and still only 86.7% with seven siblings (i.e. family of **eight**) - by no means a certainty!

For the U.K. population as a whole (average family size 2.3 children at present), about 31% of people (just under a third) will have a tissue-type-matched sibling

This leaves 69% of the population with no suitable fully-matched brother or sister available as a bone marrow or blood stem cell donor for conventional transplant

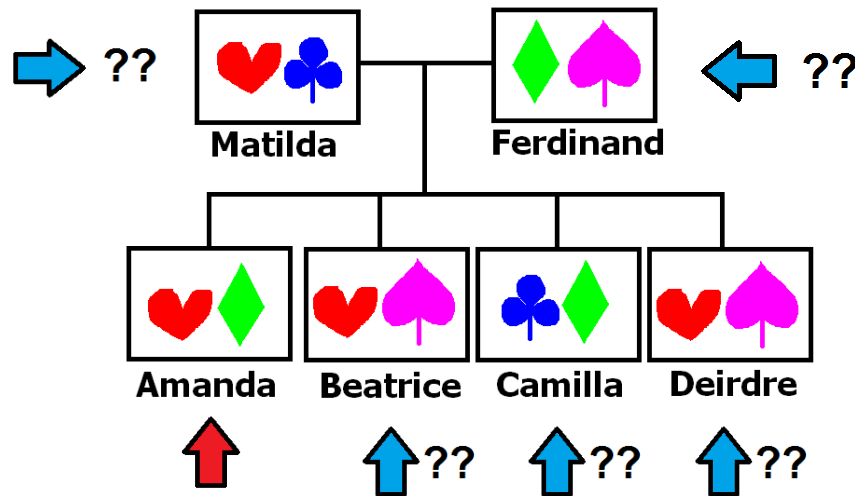
For most patients (around 90%), it is possible to identify a suitable 10/10 or 9/10 HLA matched Volunteer Unrelated Donor from registries worldwide

For the remaining 10%, the only options are either Umbilical Cord Blood transplant or haploidentical transplant

HPC transplant – Seattle; Shanghai;Glasgow?

- HPC transplant was initially pioneered by large US HPC transplant centres such as Seattle
- It was then taken up enthusiastically in China, where most of the population have no siblings due to the One Child Policy, and where there is no routine access to VUD registries
- Somewhat to everyone's surprise, published outcomes were almost as good as from conventional transplant using a fully HLA-matched donor
- In the last 5 years, haploidentical transplant has been introduced to UK allogeneic HPC transplant centres, including Glasgow
- Initially, this was done as part of a study, "UK Haplo study", but due to good initial outcomes haplo transplant has now progressed into routine clinical use over the past year to 18 months
- The Glasgow CAU has been asked to assess all the prospective haplo donors for patients being transplanted in Scotland, and to collect PBSC or bone marrow from the preferred haplo donor

Haploidentical HPC transplant – why is it a problem as regards donor selection?



...plus potentially
nieces, nephews,
uncles, aunts &
cousins!!

- Amanda is 32 years old, has high-risk AML in second CR and needs a transplant
- However, she has an unusual tissue type and has no suitable VUD or umbilical cord donor available
- She also has no matched sibling available
- However, all three of her sisters, plus both parents, are haploidentical – **who should we choose?**

A typical haplo donor selection algorithm

Confirm whether each donor is willing and medically fit to donate



Then prefer children > siblings > parents > nephews or nieces > uncles or aunts > cousins



Then prefer CMV matched donor over CMV mismatched donor



Then male donor over female



Then ABO blood group match over mismatch *

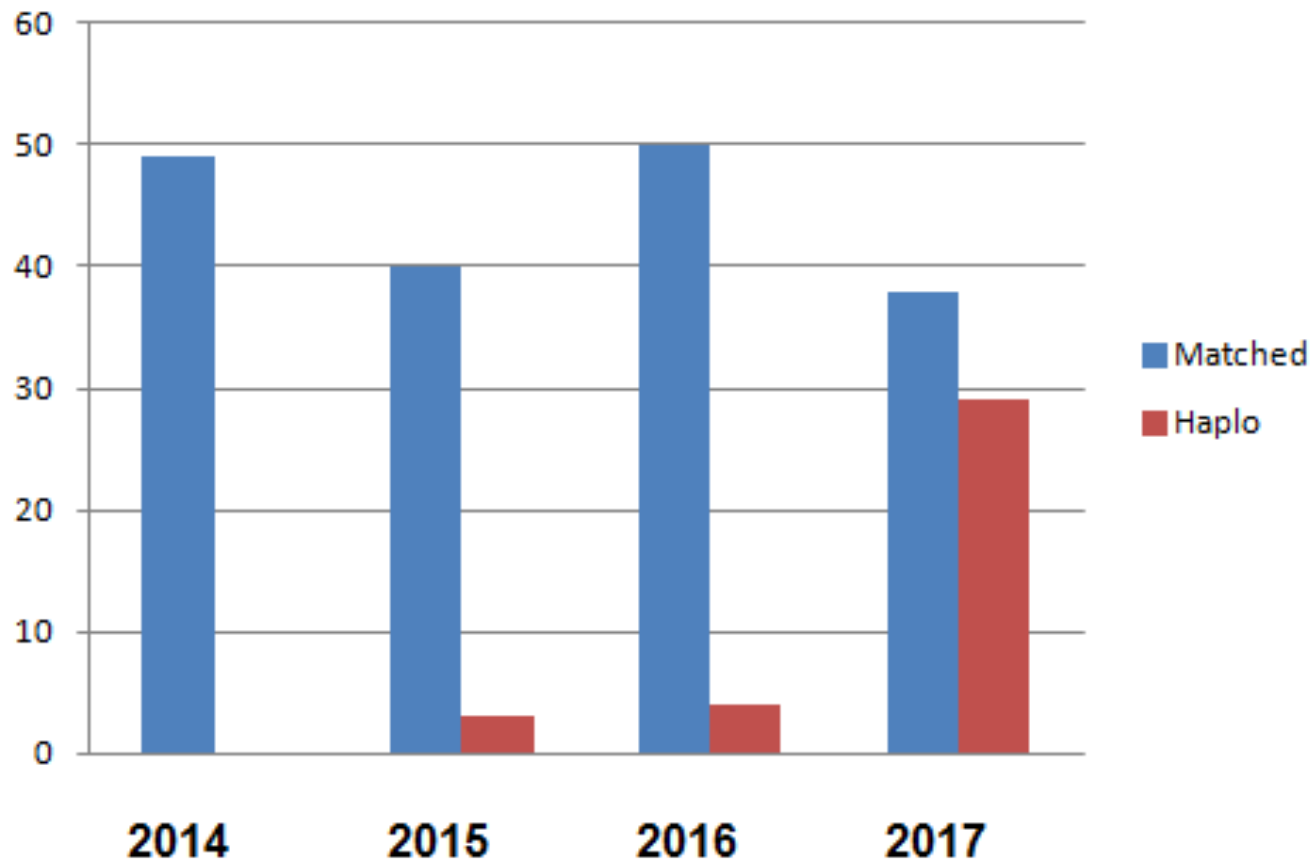


Then go by weight (choose the heaviest)

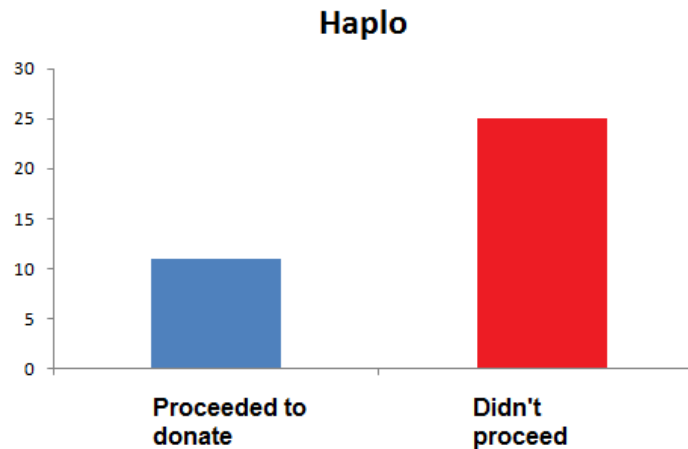
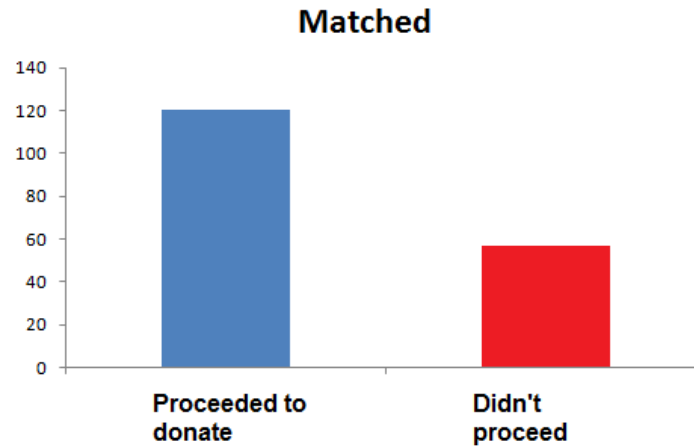
* Blood group higher up the algorithm if using bone marrow rather than PBSC, due to need to red-cell-deplete the product

- But, how do we know whether a prospective donor is willing and medically fit to donate without seeing them?
- We do already have a postal tissue typing system in place for geographically remote donors, that involves initial donor health screening by phone
- Getting tissue typing blood samples taken by GPs, and sending them to the Glasgow TT lab by post, has historically proven to be feasible
- However, we had **not** historically attempted to get blood group or CMV testing done by post
- Initially, we therefore had to see **all** prospective haplo donors in person for donor counselling and assessment, when asked to find a haplo donor for a particular patient

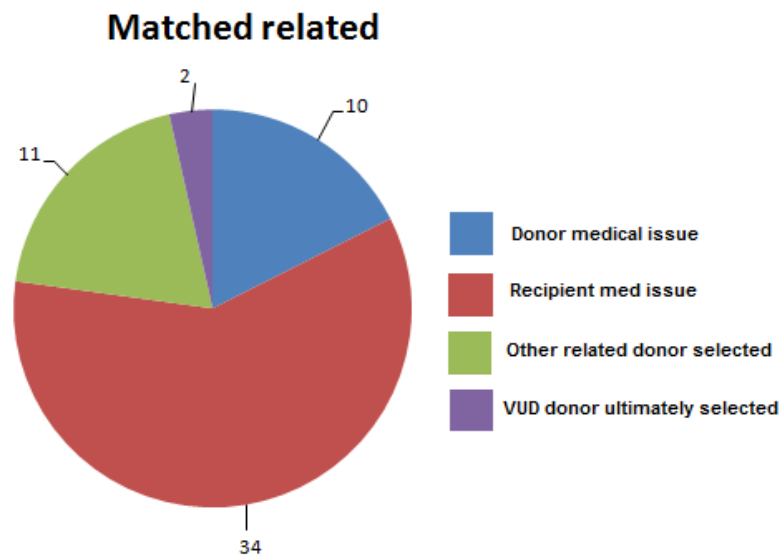
Recent sharp upturn in prospective haplo donors attending CAU Glasgow for assessment



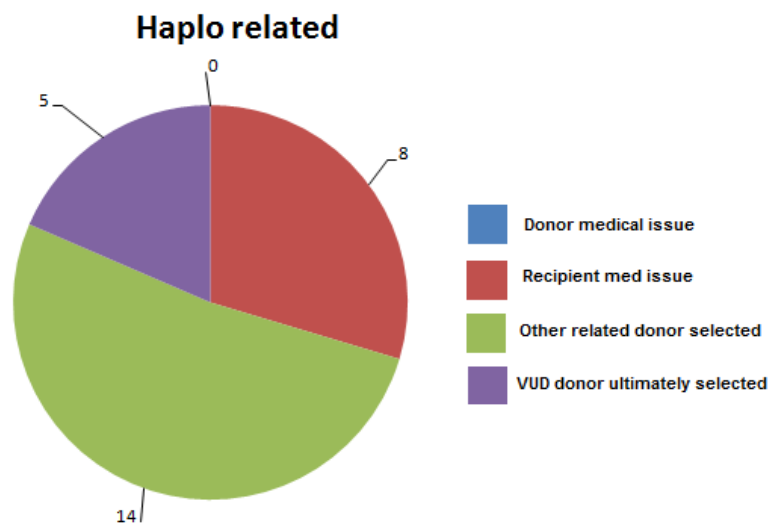
Far fewer haplo donors seen for assessment actually proceeded to donate, compared to matched sibs



Reason for haplo donors not proceeding to donate was most commonly that another family member was selected instead



Data are for all prospective adult HPC donors seen for assessment at CAU Glasgow, 2014-2017 inclusive



Haplo transplants generate more than twice as much work for CAU staff per transplant, compared to matched-sib transplants

Matched-sib transplants:

Donors assessed per donation actually proceeding = $(177/120) = 1.5$ approx

Haplo transplants:

Donors assessed per donation actually proceeding = $(36/11) = 3.3$ approx

Admin staff (i.e. the CAU Secretary) bear the brunt of any additional allo donor workload

Allo donor work carried out per donor by CAU medical staff:

- First visit – 1.5 hours medical time approx
- 2nd visit – 30 mins medical time approx
- Dictation of various correspondence – 30 mins medical time approx

Available staff: 1 Consultant; 1 Specialty Doctor; 1 rotating Haem Registrar

Allo donor work carried out per donor by CAU nursing staff:

- Tissue typing blood sampling – 5 minutes
- 1st and 2nd visit blood sampling – 15 to 20 minutes

Available staff: approximately 7 WTE CAU Nurses

Allo donor work carried out per donor by CAU Secretary: estimated 3 to 4 hours' work per donor

- Initial letter re tissue typing
- TT results letter
- Assessment visit summary letter to BMT Consultant
- Letter to donor's GP following assessment visit
- Follow-up letter to donor following assessment visit
- Arrangement of travel and accommodation for assessment visit, 2nd visit and actual donation
- Reimbursement of the above
- Copious Email / phone interactions with donor and BMT team regarding logistics of actual donation

Available staff: one overstretched CAU Secretary

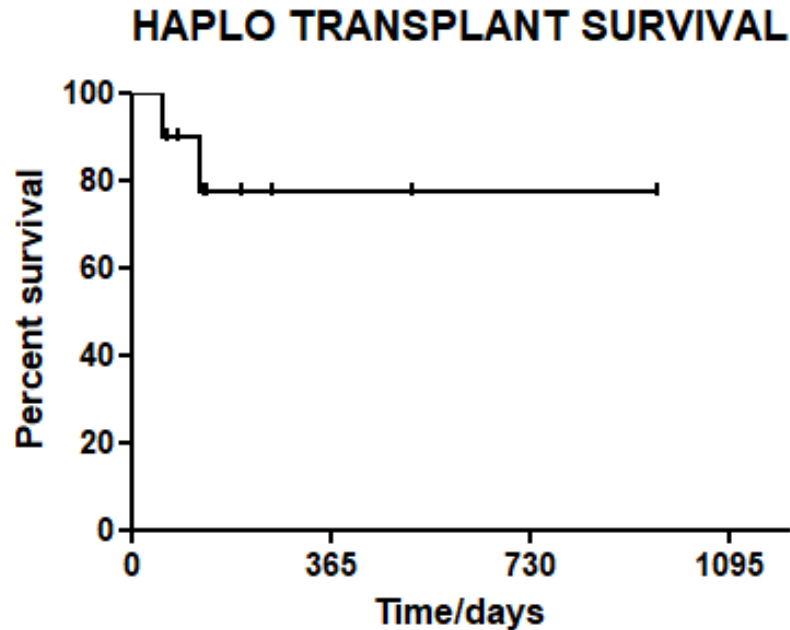
Our current solution: initial prospective Haplo Donor 'mini-assessment', potentially involving GPs for geographically remote donors

- We now attempt a cut-down 'mini-assessment' for prospective haplo donors, comprising a brief medical history (which may be taken by phone), weight, and blood samples for tissue typing, blood group & CMV serology
- Only the most promising donor in the family then attends CAU Glasgow for full face-to-face counselling and assessment
- If at all possible, we ask prospective donors to attend CAU in person for the 'mini-assessment'
- More than 50% of prospective donors stay within reasonable travelling distance of Glasgow
- However, others are geographically remote (potentially anywhere in the world)
- For UK donors not within reasonable travelling distance of Glasgow, we are now trying to ask GP practices to take blood samples not only for postal tissue typing (historical system in place), but also for postal CMV typing and blood grouping (much more challenging!)
- CAU Secretary still likely to be involved in liaising with GPs and/or other RTCs to collate results of 'mini-assessments' to help medical team to select the preferred donor
- However, this has cut down substantially on workload, particularly on the Admin side

Has it all been worth it?

- Hopefully yes!
- 12 adult patients have received haplo transplants to date in Glasgow
- Median recipient age at transplant = **59.5 years** (range 25-67 years), i.e. a relatively high-risk population
- Recipient gender distribution was: male (n=7), female (n=5)
- Donors were brothers (n=6), sisters (n=2), sons (n=2) or daughters (n=2).
- **Overall Survival and Progression-Free Survival are both 83% at median 9 months of follow-up**
- This compares very favourably with outcomes of fully-matched sibling allograft (both at our own centre, and published outcomes from EBMTR/CIBMTR data)
- Diagnoses were: AML or AML/MDS (n=6), ALL (n=3), T cell NHL (n=1), T-PLL (n=1) or blast phase MF (n=1)

Overall Survival



- One patient (with blast phase myelofibrosis) died of relapsed disease
- One patient died of GvHD plus sepsis after stopping ciclosporin early (due to VOD with renal failure)
- The remaining 10 patients are alive at median 9 months follow-up

What have we learned?

- Haplo transplant **is** worth the effort
- However, centres carrying out haplo donor assessment should not attempt to replicate the exact approach used for **matched** related donor counselling & assessment, otherwise the workload of assessing multiple prospective donors for a single recipient is likely to be excessive
- The approach of **initial “mini-assessment”** of prospective haplo donors is now working well for us
- Pick one haplo donor who looks best on paper on the basis of age, gender and (if available) blood group & CMV, and preferably see only that one donor for **full** donor assessment, at least to start with
- Outcomes are best using an adult child of the patient as the donor
- However, **take care with children donating for their mother** – mum often has HLA antibodies against paternally derived HLA antigens!

...And what about the actual cell separator machine stuff?

- Even if not involved directly in donor selection and assessment, haplo transplant is eventually likely to impact on all apheresis services undertaking allogeneic PBSC collection
- We have seen our related allo donor PBSC collection workload increase by an estimated 25% due to collection of haplo donors, for recipients who would otherwise have received either suboptimal VUD transplant, or cord transplant
- The actual PBSC collection is not significantly different from collection of PBSC from an allo donor for conventional fully-HLA-matched transplant
- Donors are quite often children of the recipient: subtly different donor-recipient dynamic than for siblings, but children are usually highly motivated to donate
- Centres who do a lot of haplos are starting to use second-degree relatives as donors, e.g. nephews or first cousins – likely to have a less close relationship with the recipient – needs more research into the psychology etc, particularly risk of family coercion
- Target PBSC dose is often fairly precise – ideally $5 \times 10^6/\text{kg}$ recipient weight for RIC haplo – not much more and not much less!
- CD34+ dose prediction formulas are helpful
- Most of our haplo donors have still only needed one day on the machine

Special thanks to everyone who helped:



Our amazing team of Apheresis Nurses:

Joy Sinclair (Apheresis Charge Nurse)
Colette Currie, Sharon Robertson, Lorna Jackson, Lisa Kean, Louisa Wood, Joanne Lowrie, Veronica Lafferty & Jocelyn Lustre

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Dr Dave Irvine
Dr Anne Parker, Dr Grant McQuaker,
Dr Anne-Louise Latif, Dr Igor Novitzky-Basso

BMT Nurse Coordinator:

Helen Hunter

Our still-overworked but never-stressed temporary CAU Secretary:

Rhona Auchincloss

....And special thanks to Dr Dave Irvine for producing a Kaplan-Meier curve with approximately 3 femtoseconds' notice!!