Factors Influencing Haematopoietic Progenitor cell transplant outcome

Optimising donor selection

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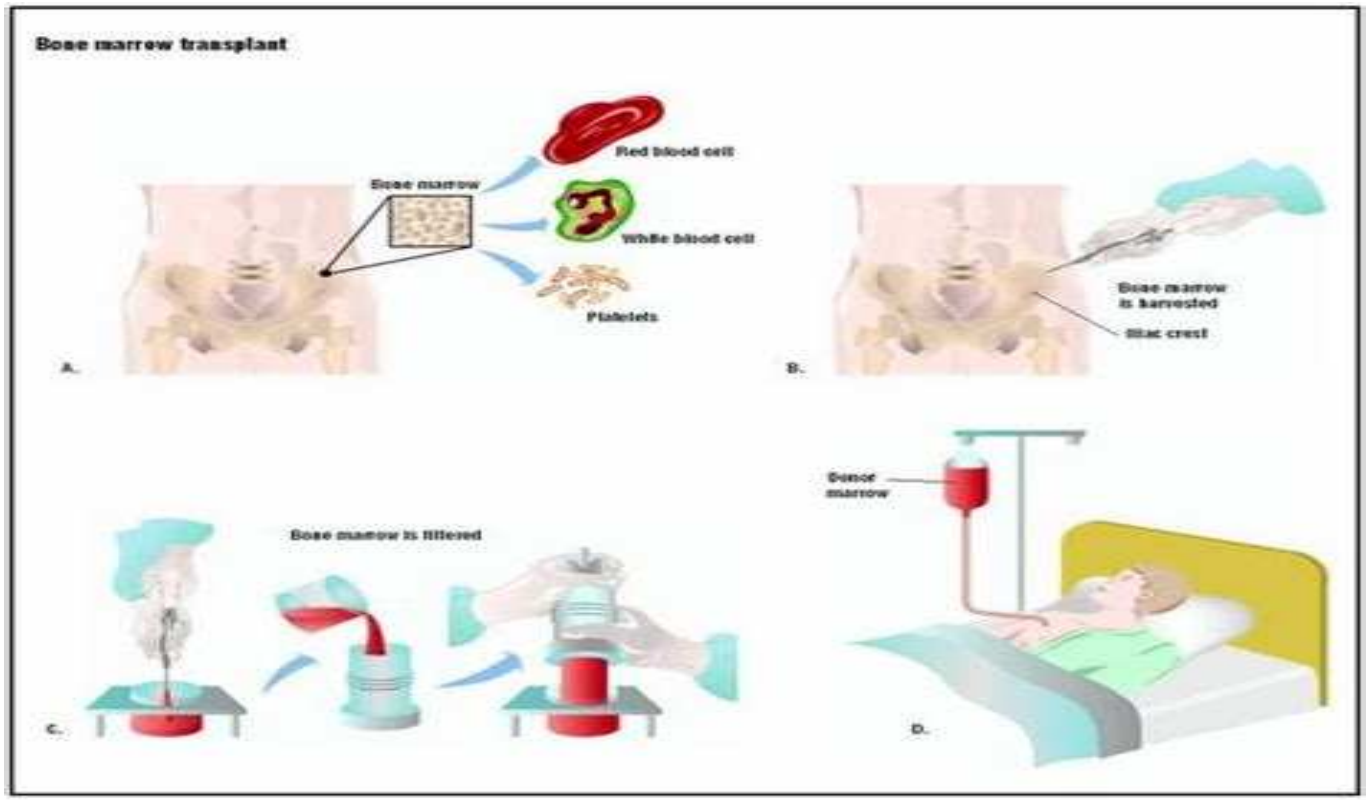
Haematopoietic progenitor cell transplants (HPCT)

-The infusion of donor derived bone marrow stem cells that can repopulate haematopoietic system of the recipient



EBMT Activity Survey in 2015: Patient and transplant numbers

Indication	Allogeneic HSCT	Autologous HSCT	Total
1st allo/1st auto HSCT	16 030	21 596	37 626
Additional HSCT	1 272	3 273	4 545
TOTAL	17 302	24 869	42 171

Teams: 655 (of 687) Countries reporting: 48

EBMT Activity Survey in 2015:

Donor type and stem cell source: all transplants

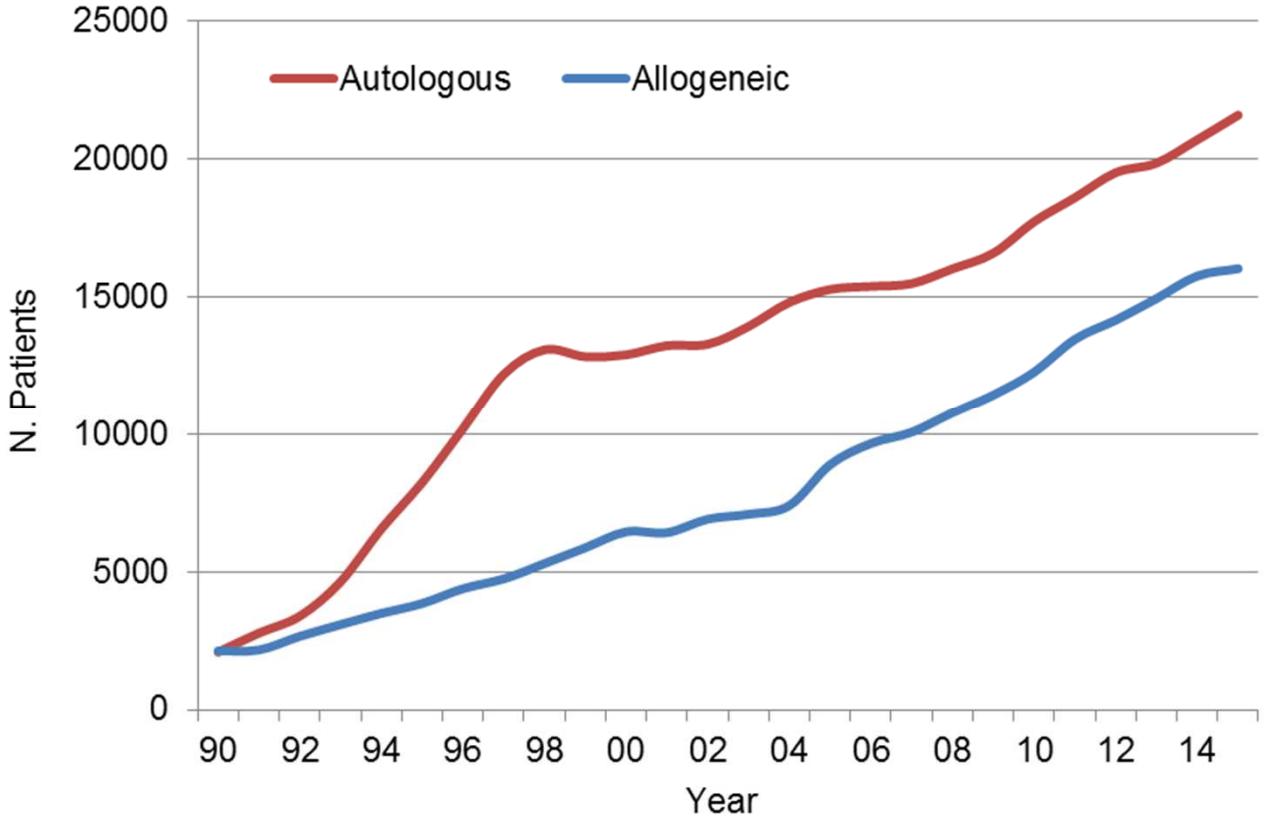
	Stem Cell Source			
Donor type	BM	PBSC	Cord	Total
HLA-id	1 489	4 359	40	5 888
HLA-non id	827	1 554	5	2 386
Unrelated	1 426	7 164	411	9 001
Syngeneic	n.a.	n.a.	n.a.	*27*
Allogeneic	3 742	13 077	456	17 302
Autologous	98	24 770	1	24 869

EBMT Activity Survey 2015: Main indications

Indication	Allogeneic 1st HSCT	Autologous 1st HSCT	Total
Leukemia	11 743	539	12 282
Lymphoma	1 574	8 143	9 717
Plasma Cell disorder	567	11 187	11 754
Solid tumor	38	1 478	1 516
Non-malignant disorders	1 985	223	2 208
Bone marrow failure	*827*	*0*	*827*
Other	123	26	149
Total 1st Transplants	16 030	21 596	37 626

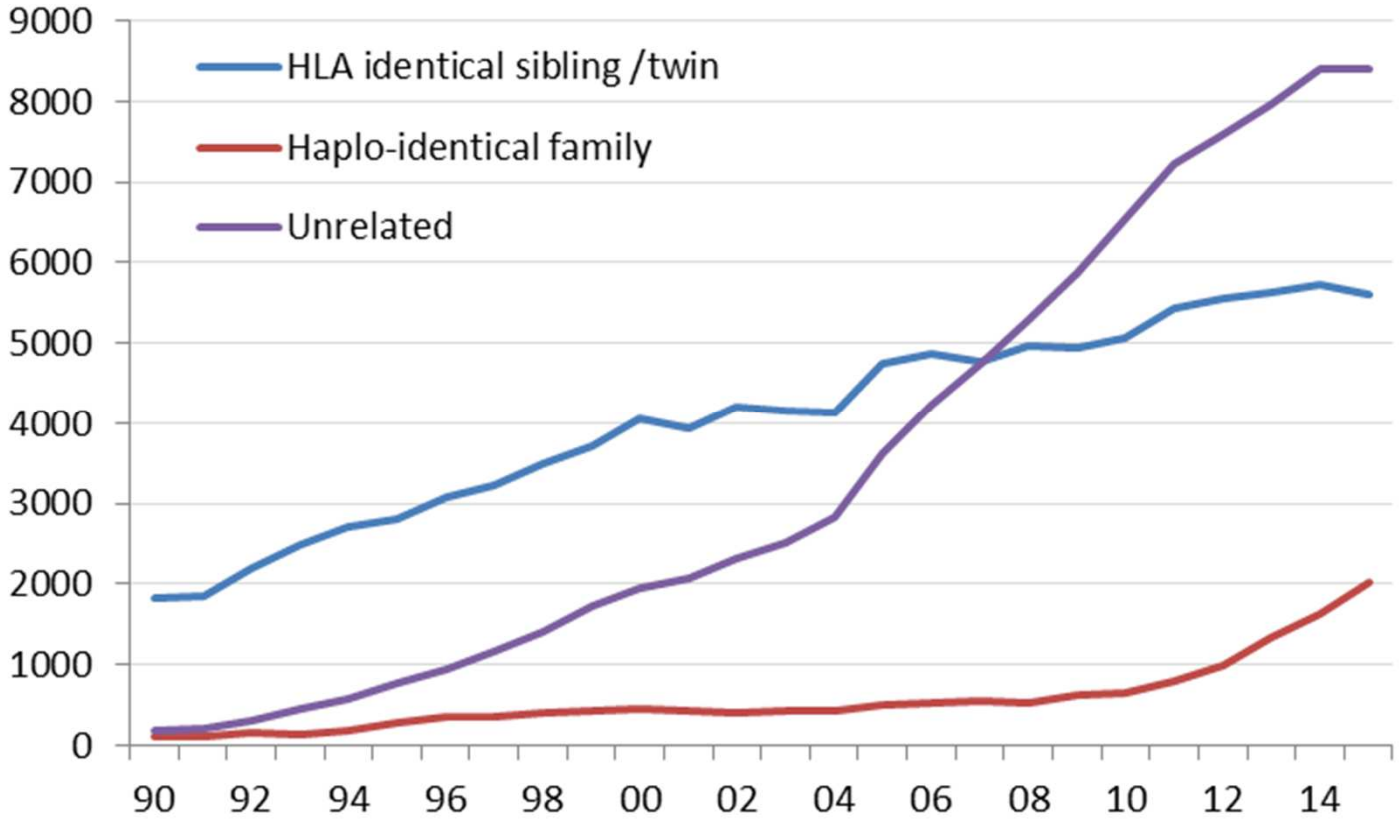
HSCT Activity in Europe 1990-2015:

Transplant type 1st HSCT



HSCT Activity in Europe 1990-2015:

Donor origin: 1st HSCT



BSHI Guidelines:HLA matching and donor selection for haematopoietic progenitor cell transplantation *A Margaret Little et al IJI , 2016*

Practices covered:

- Includes HLA typing definitions
- HLA matching and mismatching for related donor transplantation
- Unrelated donor transplantation
- Cord blood transplantation
- HLA alloantibody detection
- Non HLA factors
- CPD

The Recommendations

- Used “GRADE” nomenclature

GRADE: an emerging consensus on rating quality of evidence and strength of recommendations

Gordon H Guyatt, Andrew D Oxman, Gunn E Vist, Regina Kunz, Yngve Falck-Ytter, Pablo Alonso-Coello, Holger J Schünemann and for the GRADE Working Group

BMJ 2008;336;924-926
doi:10.1136/bmj.39489.470347.AD

Grade System

For each recommendation the quality of evidence has been graded as:

A: High quality – further research is very unlikely to change our confidence in the estimate of effect

B: Moderate quality – further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

C: Low quality – further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

D: Very low quality – Any estimate of effect is very uncertain

Grade System levels

For each recommendation the strength of recommendation has been indicated as one of:

Level 1 (we recommend)

Level 2 (we suggest)

Not graded (insufficient evidence)

HLA typing

Recommendation

All laboratories performing H&I testing for allogeneic HPC transplantation should follow EFI standards and be accredited by CPA/UKAS and EFI.

Evidence: high Strength: recommend Grade = 1a

- Verification typing

- Confirmation of HLA Homozygosity in certain conditions such as AML (Grade 2a)

HLA typing resolution

Definitions have been produced:
Blood 2011; 118(23):e180-e183
Human Immunology 2011; 72: 1214-1216

e-Blood

Definitions of histocompatibility typing terms

Eduardo Nunes,[1] Helen Heslop,[2] Marcelo Fernandez-Vina,[3] Cynthia Taves,[3] Dawn R. Wagenknecht,[3] A. Bradley Eisenbrey,[4] Gottfried Fischer,[5] Kay Poulton,[5] Kara Wacker,[6] Carolyn Katovich Hurley,[7,8] Harriet Noreen,[7] and Nicoletta Sacchi[8]

[1]American Association of Blood Banks, Bethesda, MD; [2]American Society for Blood and Marrow Transplantation, Arlington Heights, IL; [3]American Society for Histocompatibility and Immunogenetics, Mt Laurel, NJ; [4]College of American Pathologists, Northfield, IL; [5]European Federation for Immunogenetics, Department of Immunohematology and Blood Transfusion, Leiden University Medical Centre, Leiden, The Netherlands; [6]Foundation for the Accreditation of Cellular Therapy, Nebraska Medical Center, Omaha, NE; [7]National Marrow Donor Program, Minneapolis, MN; and [8]World Marrow Donor Association, Leiden, The Netherlands

Recommend that these definitions are followed and have added definition for intermediate resolution.

Evidence: high Strength: recommend Grade = 1a

"The term intermediate resolution can be applied when high resolution cannot be achieved and the provided HLA type includes a subset of alleles sharing the digits in the first field of their allele name and excludes some alleles sharing those digits.

Example include: A*02:01 or A*02:02 or A*02:07 or A*02:20 but not other A*02 alleles.

There may be cases in which the subset of alleles includes one or more alleles within a group beginning with different digits but these alleles should be the exception e.g. A*01:01 or A*01:02 or A*01:14 or A:36:04"

HLA matching

- HLA matching is the **most** important factor in most cases determining outcome of the HPCT.
- When looking for a HLA matched donor you are most likely to find a HLA match within the patient's own family (sibling donor).
- 25-30% patients find a suitable related HLA identical sibling donor.
- Consanguineous families – search in extended family

Related donor selection

HLA matched/mismatched/haplo-matched donors

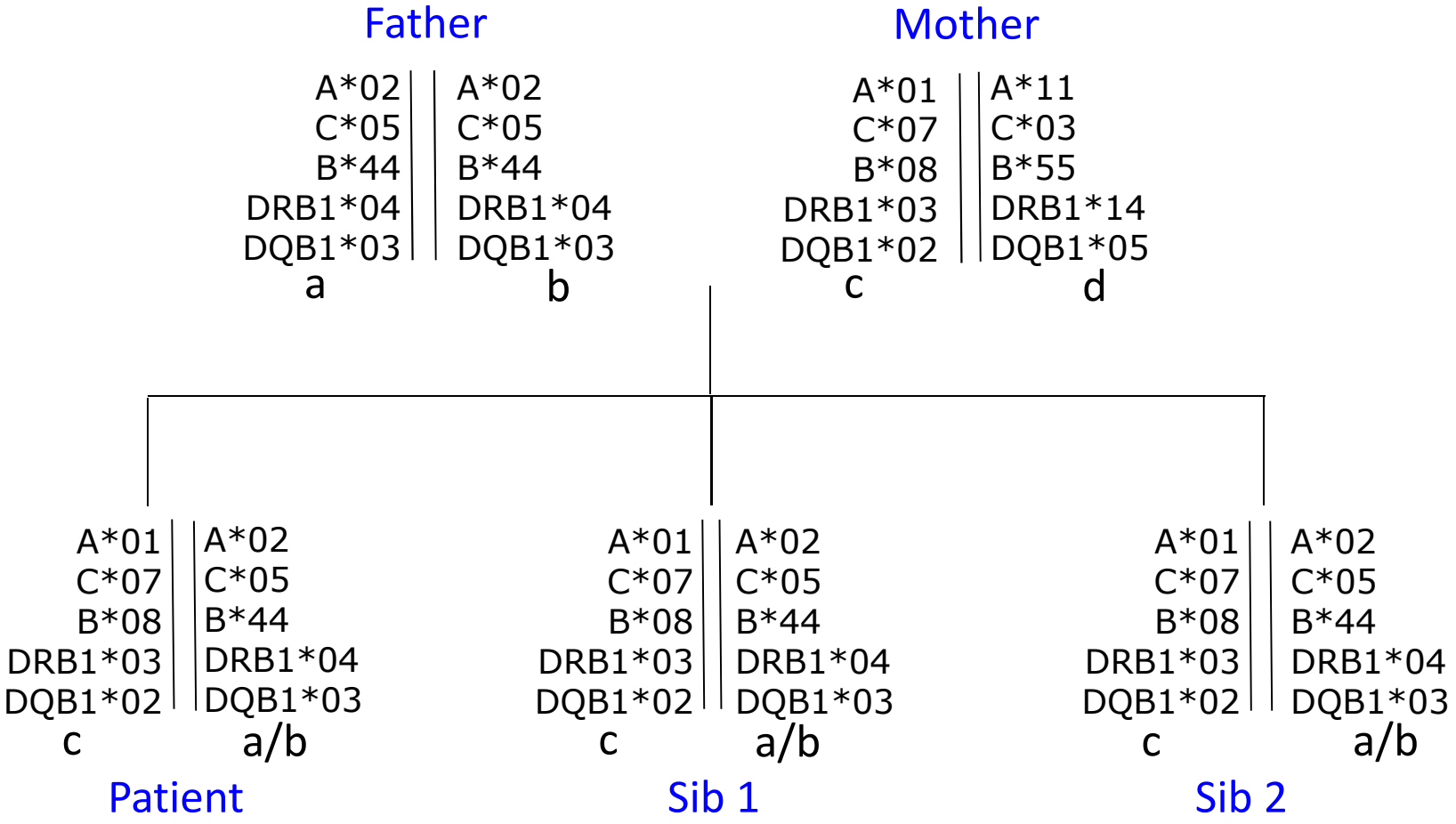
Recommendation

HLA high/allele resolution typing should be performed for related donors when haplotypes not fully identified (EFI standard)

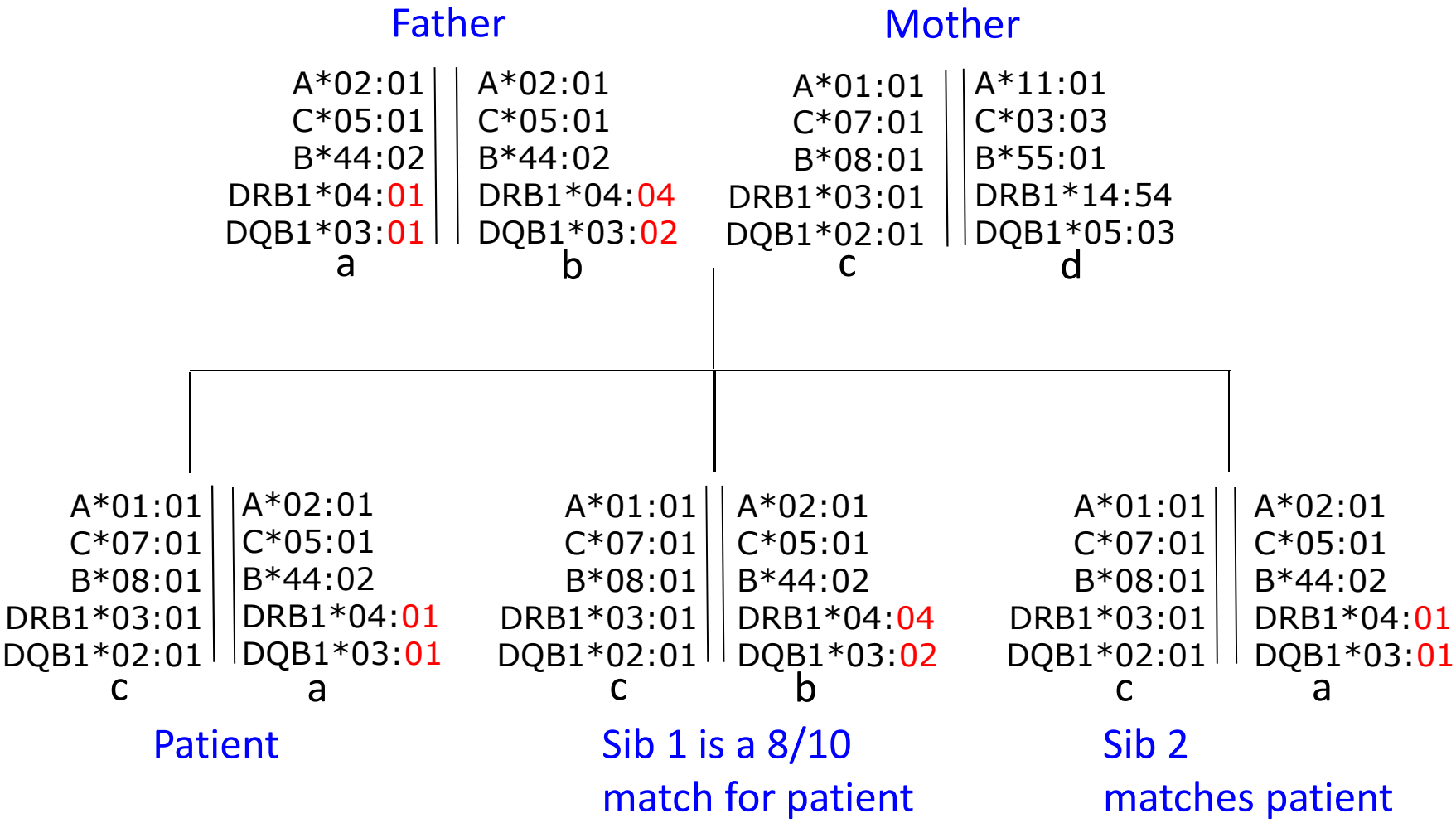
Include HLA-A,B,C,DRB1 and DQB1 (+/- DPB1)

Evidence: high Strength: recommend Grade 1a

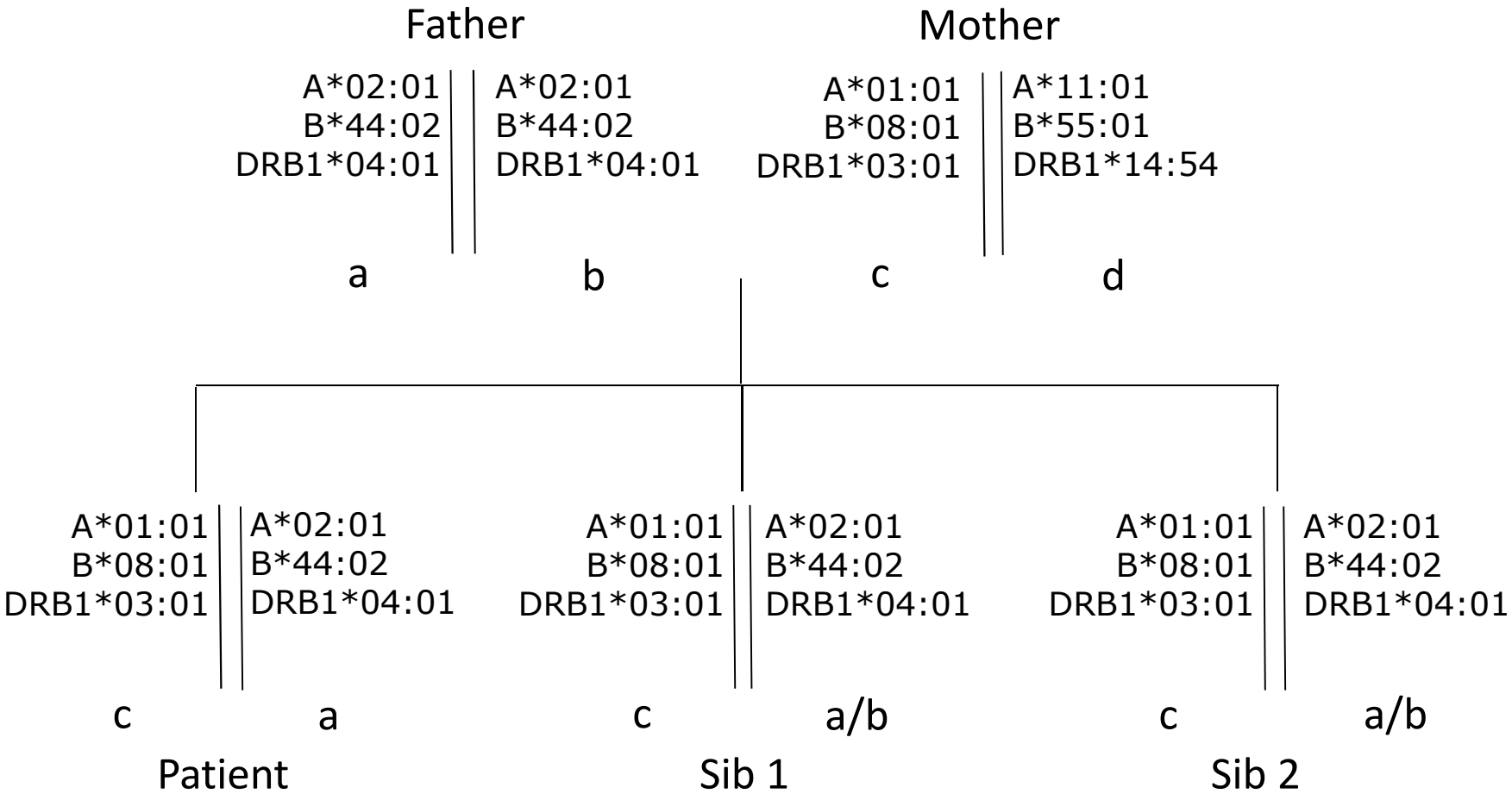
Example 1: Importance of high resolution typing



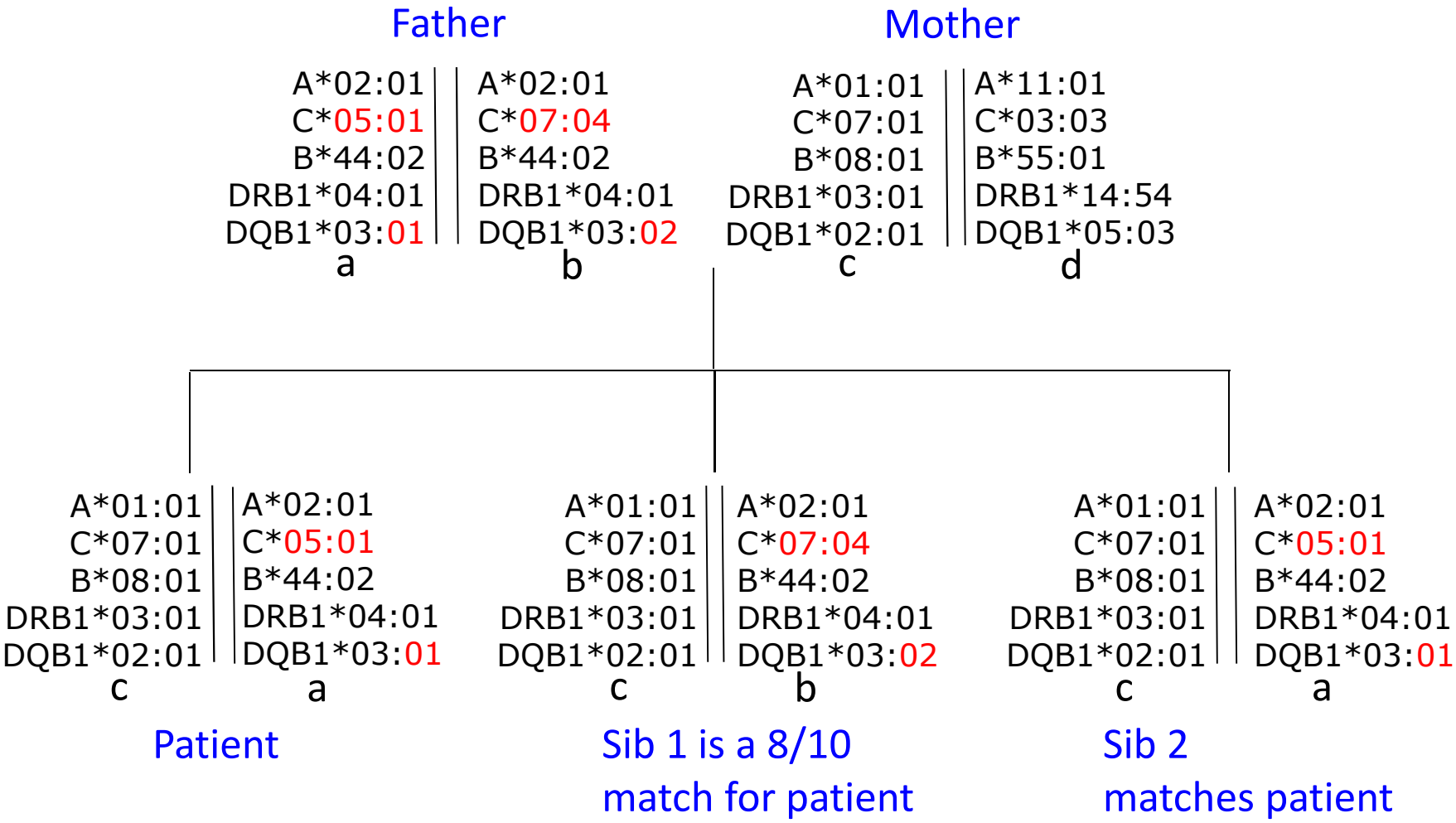
Example 1


Father
A*02:01
C*05:01
B*44:02
DRB1*04:01
DQB1*03:01
a
A*02:01
C*05:01
B*44:02
DRB1*04:04
DQB1*03:02
b
Mother
A*01:01
C*07:01
B*08:01
DRB1*03:01
DQB1*02:01
c
A*11:01
C*03:03
B*55:01
DRB1*14:54
DQB1*05:03
d
A*01:01
C*07:01
B*08:01
DRB1*03:01
DQB1*02:01
c
A*02:01
C*05:01
B*44:02
DRB1*04:01
DQB1*03:01
a
Patient
A*01:01
C*07:01
B*08:01
DRB1*03:01
DQB1*02:01
c
A*02:01
C*05:01
B*44:02
DRB1*04:04
DQB1*03:02
b
Sib 1 is a 8/10
match for patient
A*01:01
C*07:01
B*08:01
DRB1*03:01
DQB1*02:01
c
A*02:01
C*05:01
B*44:02
DRB1*04:01
DQB1*03:01
a
Sib 2
matches patient

Importance of including HLA-C and DQB1



Example 2


Father
A*02:01
C*05:01
B*44:02
DRB1*04:01
DQB1*03:01
a
A*02:01
C*07:04
B*44:02
DRB1*04:01
DQB1*03:02
b
Mother
A*01:01
C*07:01
B*08:01
DRB1*03:01
DQB1*02:01
c
A*11:01
C*03:03
B*55:01
DRB1*14:54
DQB1*05:03
d
A*01:01
C*07:01
B*08:01
DRB1*03:01
DQB1*02:01
c
A*02:01
C*05:01
B*44:02
DRB1*04:01
DQB1*03:01
a
Patient
A*01:01
C*07:01
B*08:01
DRB1*03:01
DQB1*02:01
c
A*02:01
C*07:04
B*44:02
DRB1*04:01
DQB1*03:02
b
Sib 1 is a 8/10
match for patient
A*01:01
C*07:01
B*08:01
DRB1*03:01
DQB1*02:01
c
A*02:01
C*05:01
B*44:02
DRB1*04:01
DQB1*03:01
a
Sib 2
matches patient

Haplo identical transplants

- Use of a single haplotype identical family member
- Pioneered by Perugia and Frankfort groups
- Megadose of stem cells
- PT administration of cyclophosphamide to destroy actively proliferating alloreactive lymphocytes- reduce GvHD caused by HLA mm.

Haplo transplants

- High resolution HLA typing within the family
- All at least 5/10 match
- Additional matches not beneficial (185 Tx for haematological malignancies- *Kasamon et al, 2010)*
- Mismatching for HLA proteins (eg HLA-C) that interact with different NK cell inhibitory receptors (KIR) initiate a GvH NK cell mediated alloreaction
- Covered in later talk.

Haplo donor selection criteria

- NIMA- non inherited maternal antigens via placental trafficking of maternal and foetal cells during pregnancy.
- Tolerance to these antigens when present on HPC transplanted into patient. Reduces HvG immune response.
- Various studies have suggested mother optimal donor, father optimal donor or sibling
- Insufficient evidence in literature to support use of one over the other.
- Multiple Haploidentical donors available select donor on non-HLA factors such as CMV status

Related donor selection

Haplo-identical transplants

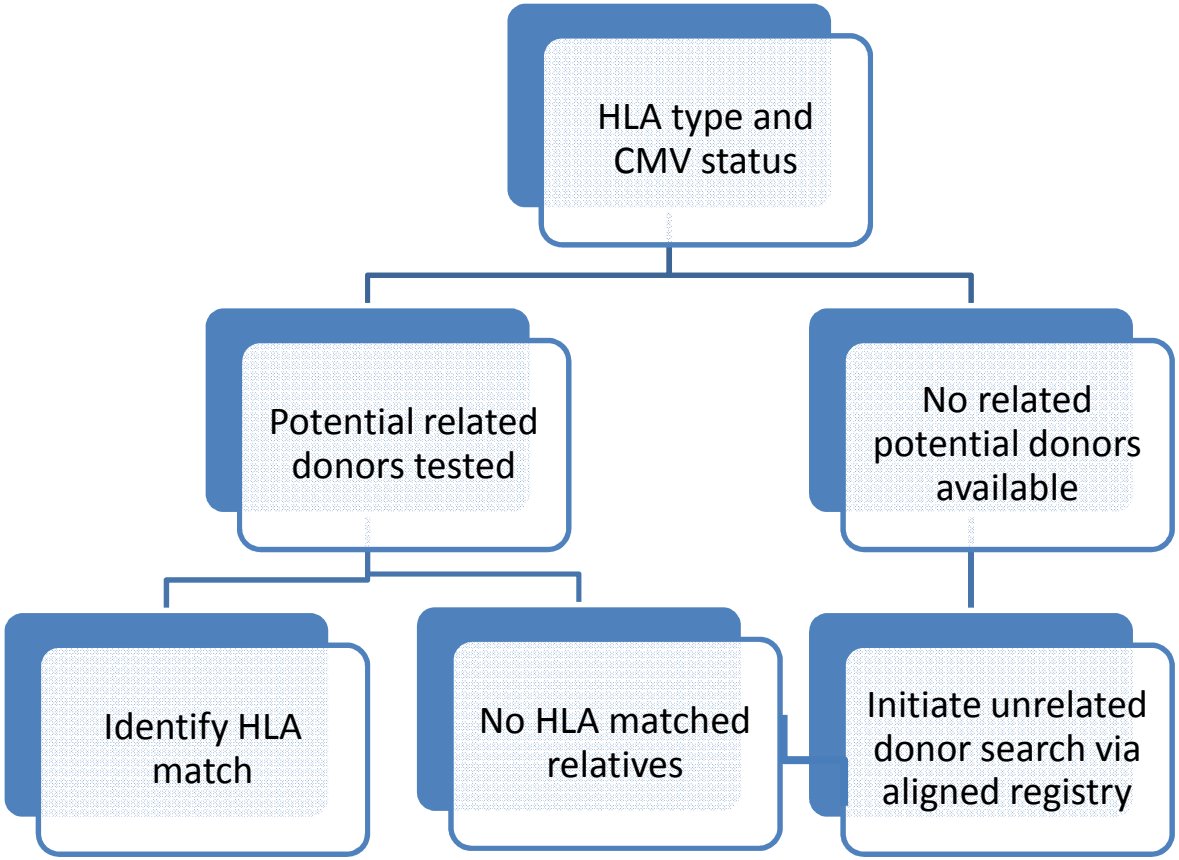
NIMA

- Role in tolerance reducing HvG response
- Evidence variable,
- Evidence: Low Strength: Not graded

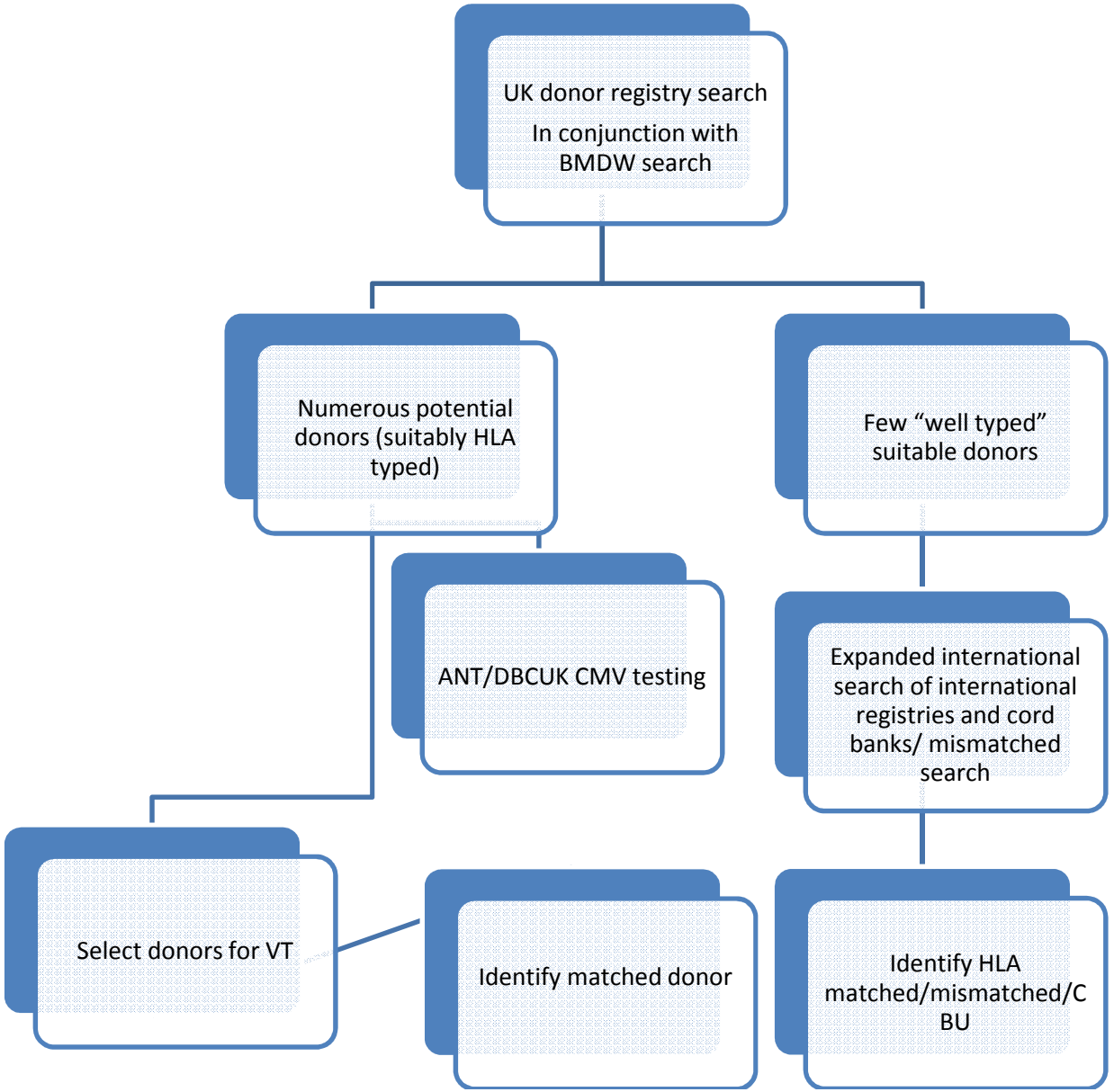
NK cell receptor typing

- Role in GvL suggests mismatching for KIR ligands
- Evidence variable,
- Evidence: Low Strength: Not graded

Donor Search Process



Unrelated donor search process



Unrelated donor selection

- Registries are working hard to increase the number of donors
- improving the resolution of HLA types (NGS, TGS)
- typing donors for multiple HLA loci

The most useful search results are obtained when the patient has been HLA typed to high/ allele level resolution as this allows elimination of mismatched donors

<u>Recommendation</u>

The patient should be high/allele resolution typed (HLA-A,B,C,DRB1,DQB1) prior to submitting the HLA type for an unrelated donor search:

Evidence: high Strength: recommend Grade: 1a

HLA matching for unrelated donor selection

Identify the best HLA match available

Matching for HLA-A,B,C,DRB1(+DQB1) improves outcome – multiple studies in agreement

Role of DQ

- Not important within US studies (unless additional mismatch)
- Not unimportant within European studies

Recommendation

A 10/10 (HLA-A,B,C,DRB1,DQB1) matched donor should be selected when possible

Evidence: high Strength: recommend Grade: 1a

Knowledge of HLA associations and haplotypes frequencies

HLA haplotypes and linkage disequilibrium- HLA-B/C and DR/DQ associations - are they common or not?

Presence of a rare HLA allele or association will reduce chances of finding a matched donor –patient high resolution typed before donor search
bioinformatics.bethematchclinical.org (NMDP)
Allele frequencies.net

Algorithms used by donor registries

Use of BMDW online matching tool and other online tools -IMGT

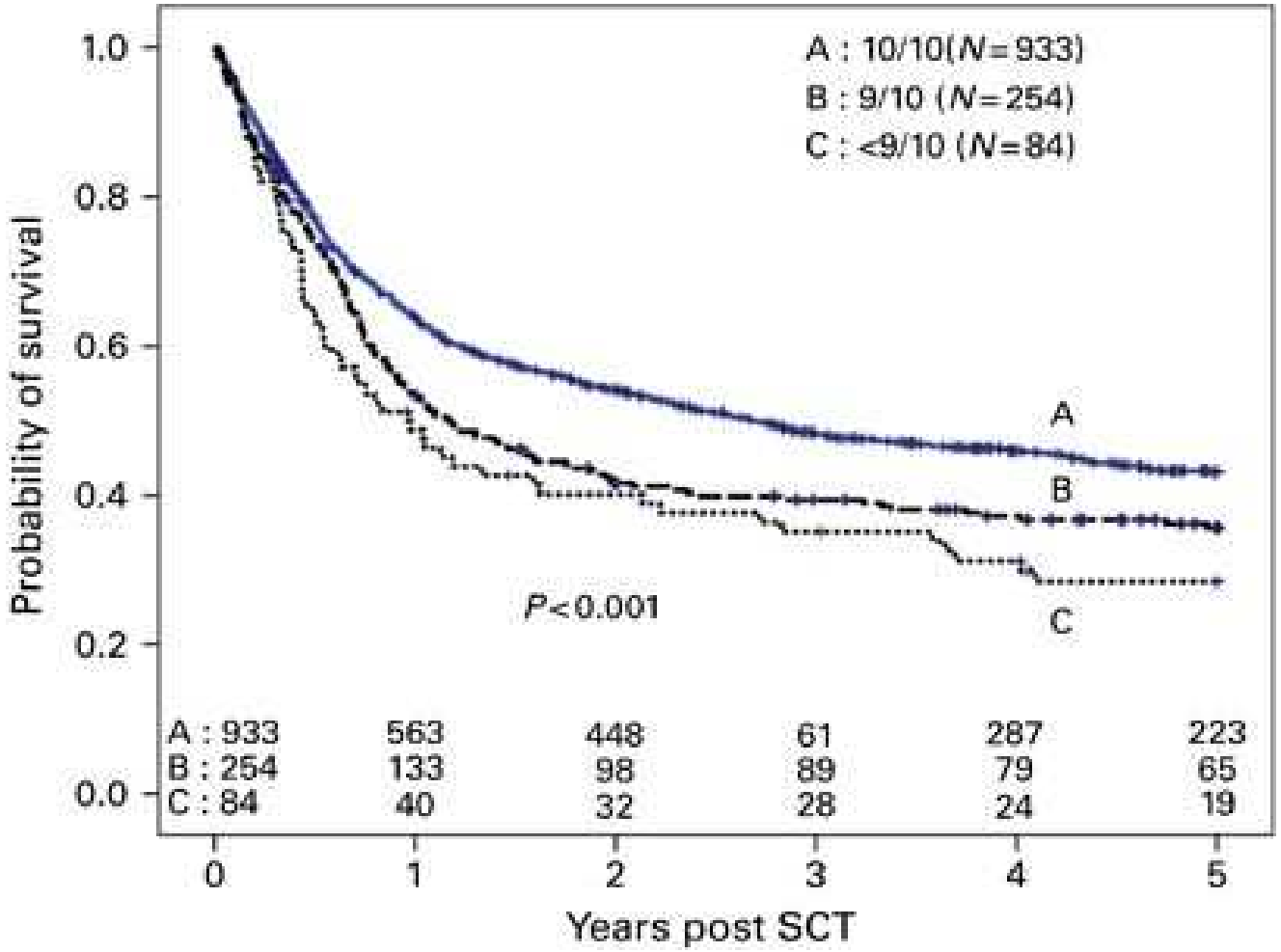
The H & I specialist must advise on the likelihood of finding a high resolution matched donor within the time frame defend by transplant team.

HLA mismatching

- 10/10 transplants have better overall survival
- Different studies show different impact of single mm at individual loci.
- Complexity of HLA polymorphism means not all mm at a given locus are equal.
- Mismatches at a given locus may involve different number of aa mm.
- Not all mm at a given locus will have equal effects of GvL and HvG responses.

Survival curves HLA matching status

Shaw et al, 2017



HLA mismatching

- Role of DQB1* matching. *Lee et al, 2007*
- Data from 3857 transplants. Individual mismatches for DQB1* had no impact on survival.
- However, an additional mismatch at HLA-A,-B, -C, DRB1.

  Poorer survival. Not statistically significant.
- HLA-C- certain C mismatches may be more permissible due to level of expression (C*03:03 and C*03:04)- *Fernadez Vina et al 2014*
- Studies have looked at the impact of aa substitutions on transplant outcome (acute, chronic, TRM, relapse and OS) aa substitutions at binding positions.
- Guidelines say when a choice of mm donors is available can use mm aa residue data and HLA-C expression to select donor of choice.

Which HLA loci mismatches are most (or least) detrimental?

No consensus

Variability in outcomes reported attributed to differences in study design, patient demographics including ethnicity, source of stem cells, era of transplant etc.

Mismatching for either HLA class I or class II alleles can affect outcome.

Mismatching for antigen or allele can affect outcome

Recommendation

In the absence of a 10/10 matched donor, a single mismatch for any HLA-A,B,C,DRB1,DQB1 is acceptable.

Evidence: high Strength: recommend Grade: 1a

Impact of HLA-DP mismatching

- Recombination hotspot – DQB1* and DPB1*
- 5% of otherwise 10/10 matched siblings are DPB1* mm.
- DPB1* specific T cells detected and associated with GvL and GvHD *(Stevanovic et al, 2003)* – direct role of HLA-DP proteins in the immune responses between patient and donor cells post HPCT.
- Earlier studies allelic DPB1* mm offer GvL advantage via a reduction in relapse , increase a GvHD and increase in mortality *(Shaw et al, 2007).*
- May be due to level of expression *(Petersdorf et al, 2015)*

Permissive Vs non permissive DP mm

- HLA-DPB1* mm assigned as permissive or non – permissive.
- Based on immunogenicity to T cell epitopes *(Crocchiolo et al , 2009)*
- In unrelated donor HPCT recipients with permissive DPB1*mm had a significantly higher 2 year survival
- (55% vs 39% p=0.005). Decrease in NRM
- Data from ANT (in press) *Meyer et al* on impact of permissive and non permissive DP matched donors

HLA-DP

HLA-DPB1 typing should be performed and when a choice of equally well matched donors is available, non-permissive mismatches should be minimised:

Evidence: low Strength: suggest Grade: 2c

HLA-DRB3,4,5

HLA-DRB3,4,5 typing should be performed and when a choice of equally well matched donors is available, mismatches should be minimised

Evidence: low Strength: suggest Grade: 2c

Direction of mismatch

HvG mismatches are favoured over bi-directional and GvH mismatches.

Evidence: low Strength: suggest Grade: 2c

Factors that Influence outcome

- Outcome measures:Patient survival, disease free survival, relapse, GvHD
- **Donor factors**
  - Related v unrelated
  - Age
  - CMV status (blood group)
  - HLA match v's HLA mismatch-permissive/non permissive DPB1* mm
  - Other genetic factors such as KIR
  - BM v PBSC v CB
  - Male v female
  - DLI available

Selection Criteria-Sources of Stem cells

Progenitor cell selection criteria	BM	PBSC	UCB
HLA match	Minimum 9/10	Minimum 9/10	Minimum 4/6 Double 4/8 Single
Average time to neutrophil engraftment	15-23 days	12-19 days	22-32 days
Time to identify, HLA VT and harvest donor cells	2 months	2 months	1 month
Second donation available/DLI	Yes	Yes	No

Factors that Influence outcome

- **Transplant factors**
  - Conditioning protocol
  - Immunosuppression
  - Treatment of graft (TCD)
  - GvHD prophylaxis

- **Patient factors**
  - Type and stage of disease
  - Health of patient/comorbidities
  - Age

Timing of Transplant

Previous guideline

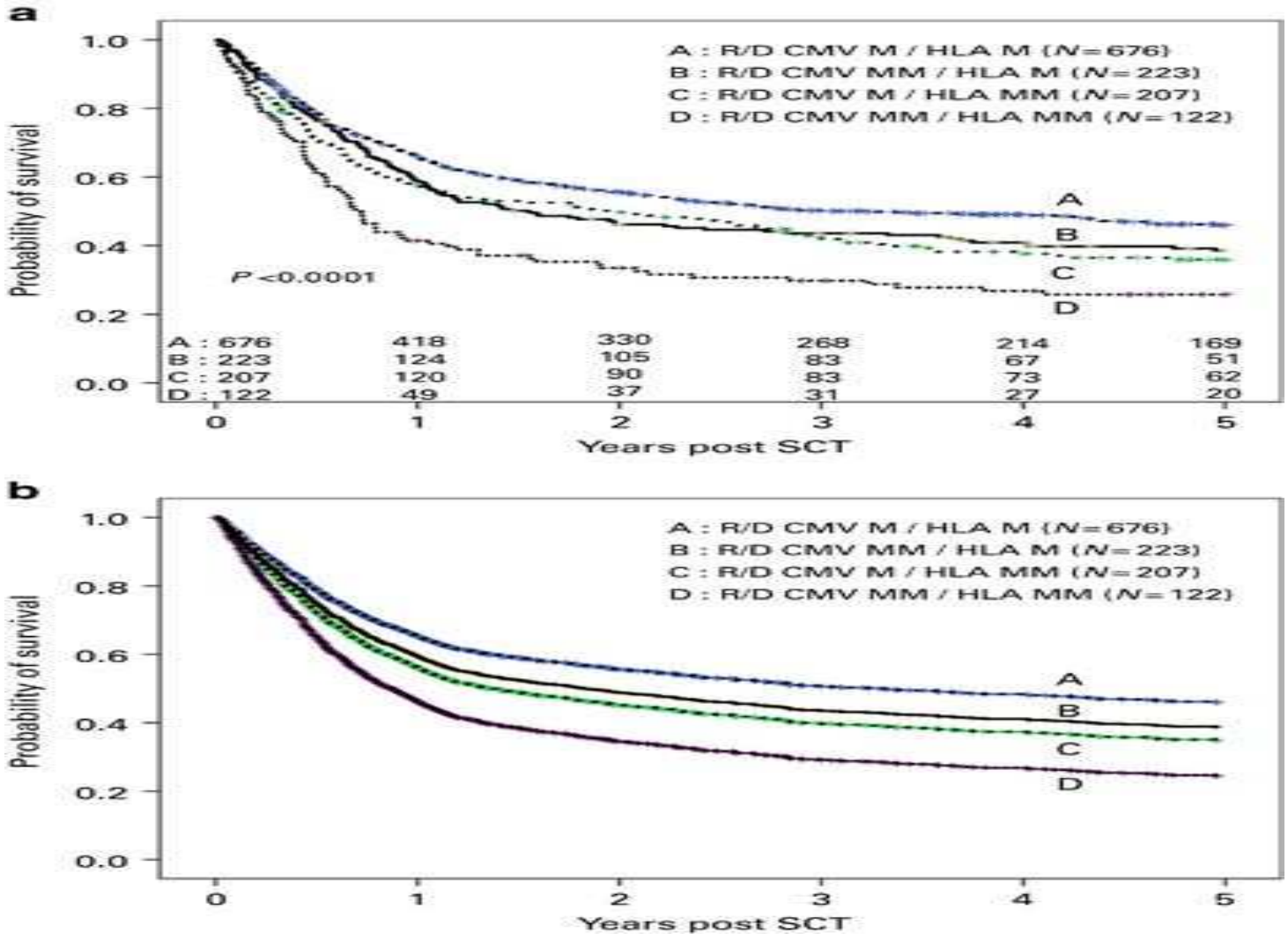
- Recommend “clinical urgency should be made available to the individual performing the related and unrelated donor search”
  - negative impact of HLA mismatching not as great for higher risk patients
  - Search for alternative donors can be expedited

Evidence: moderate Strength: recommend Grade = 1b

Cytomegalovirus

- Can cause significant complications post HPCT
- Lungs (pneumonia), Liver (hepatitis), gut (gastroenteritis)
- Major cause of morbidity and mortality in HPCT *(Ljungman et al 2014)*
- CMV matching between patient and donor should be followed. *(Emery et al 2013)*
- Evidence high Strength: recommend Grade 1a
- Effect of HLA mm may be abrogated somewhat by matching for CMV *(Shaw et al, BMT 2017)*
- CMV Matching particularly important in HLA MM transplants.

Survival curves
Recipient/donor CMV serostatus
Shaw et al 2017



Donor Age

- Younger donors should be preferentially selected when the patient has multiple HLA and CMV equally matched donors *(Shaw et al ,2017, ASBMT)*
- The publication aimed to develop a donor selection score.
- In 8/8 matched URD two large cohorts >10,000 URD transplants
- Only characteristic associated with better survival was a younger age, 2 year survival 3% better when a donor 10 years younger was selected.
- Younger donors are fitter; less likely to fail a medical

Donor Gender

- Male donors chosen preferentially where the patient has multiple HLA and CMV matched donors.
- Evidence: low Strength: recommend Grade 1c
- Some studies reported a positive effect on long term survival regardless of recipient gender (Pond et al, 2006)
- Not in *Lee et al 2007* study.

Donor Gender (cont)

- Usually larger size = higher HPC counts
- Increase in GvHD associated with female multiparous donors *(Kollman et al, 2001)*
- 2011 multicentre study showed no association between donor age, parity, and gender match with transplant outcome, only HLA *(Passweg et al 2011)*

ABO blood group incompatibility

- Major ABO incompatibilities should be avoided when there is a choice of equally matched HLA and CMV matched donors.
- Evidence: high Strength: recommend Grade: 1a
- Major and minor ABO incompatibilities do not have a significant effect on overall survival and GvHD incidence (Booth et al 2013)
- Some single centre studies show ABOi impact on clinical outcome.
- RIC with persistent recipient type ABO (PRABO) antibodies.
- Poorer overall survival (17% Vs 73%, p=0.002) Watz et al, 2014

HLA alloantibodies

- Testing at time of donor selection and if a mm donor is selected at the time of donor work up request
- If the recipient has donor directed antibodies make the clinical team aware
- Where there is a choice of donors available avoid donors to which the patient has DSA.
- Evidence: moderate strength: recommend Grade 1b
- HLA specific antibody testing in cases of failed engraftment

Selection of unrelated umbilical cord blood

- Alternative source of HPC
- Malignant and non-malignant disorders
- Delayed engraftment
- Restricted to paediatrics initially due to cell dose
- Role of allele level HLA matching between CBU and patient :1568 recipients of single CBU for haematological malignancies *(Eapen et al, 2014)*
- Related CBT – screen relative for inherited disorders for example MPS-1H (Hurler Syndrome)

CBU Selection Guidelines

- UCB units should be HLA typed to high resolution HLA-A, -B, -C, DRB1 and DQB1*

  Grade 1b

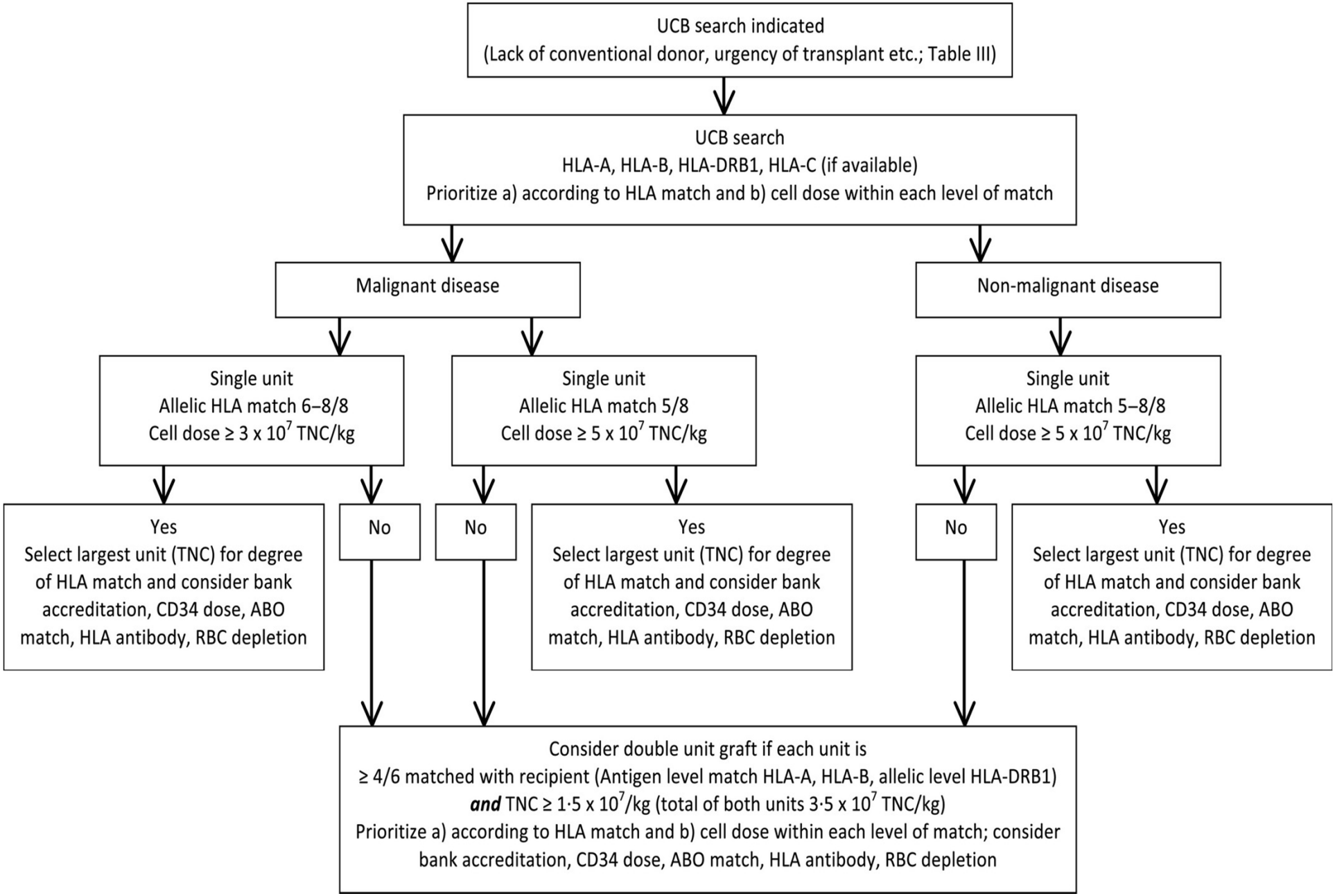
- Follow national guidelines published by *Hough et al, 2016.*
- Patients HLA antibody status when using mm CBU.

  - conflicting data *(Brunstein et al 2011, Dahi et al, 2014)*

-DSA affects neutrophil and platelet engraftment in single and double CBU setting

-Avoid CBU to which the recipient has high levels of DSA.

- Role of high resolution HLA typing not yet defined for double CBU


UCB search indicated
(Lack of conventional donor, urgency of transplant etc.; Table III)
UCB search
HLA-A, HLA-B, HLA-DRB1, HLA-C (if available)
Prioritize a) according to HLA match and b) cell dose within each level of match
Malignant disease
Non-malignant disease
Single unit
Allelic HLA match 6–8/8
Cell dose ≥ 3 x 10^7 TNC/kg
Single unit
Allelic HLA match 5/8
Cell dose ≥ 5 x 10^7 TNC/kg
Single unit
Allelic HLA match 5–8/8
Cell dose ≥ 5 x 10^7 TNC/kg
Yes
Select largest unit (TNC) for degree of HLA match and consider bank accreditation, CD34 dose, ABO match, HLA antibody, RBC depletion
No
No
Yes
Select largest unit (TNC) for degree of HLA match and consider bank accreditation, CD34 dose, ABO match, HLA antibody, RBC depletion
No
Yes
Select largest unit (TNC) for degree of HLA match and consider bank accreditation, CD34 dose, ABO match, HLA antibody, RBC depletion
Consider double unit graft if each unit is
≥ 4/6 matched with recipient (Antigen level match HLA-A, HLA-B, allelic level HLA-DRB1)
and TNC ≥ 1·5 x 10^7/kg (total of both units 3·5 x 10^7 TNC/kg)
Prioritize a) according to HLA match and b) cell dose within each level of match; consider bank accreditation, CD34 dose, ABO match, HLA antibody, RBC depletion

Selection Summary

- HLA matching based on HR typing HLA-A,-B,-C,-DRB1
- Select 8/8- matched CBU. TNC dose > 3 x 10^7/Kg
- 7/8. HLA-A or B mm preferable to DRB1
- TNC dose > 5 x 10^7/Kg for 5-7/8 matched units
- 4/8 if no other option > 5 x 10^7/Kg
- 3/8 not recommended
- Double CBT 4/6 intermediate HLA typing at HLA-A and -B and HR DRB1.
- Role of HR typing not defined for double CBT yet

Extended CBU report

- Patient's weight
- Request detailed extended unit report on shortlisted units
- Information on viability testing
- method for volume reduction/Volume cryopreserved
- Age of unit
- Bank accreditation status
- CFU –evaluate functional capacity HPCs

Other Considerations for CBT

- Red cell status – avoid replete units
- FACT/netcord accreditation- product quality indicator
- CD34+ cell dose- Good correlation with outcome
- Direction of HLA mm-GvH, HvG data inconsistent
- ABO incompatibility- data inconsistent
- NIMA mm Vs 6/6 data- Rubenstein data
- No requirement for inter unit matching
- Segment available for verification typing?

Thank-you