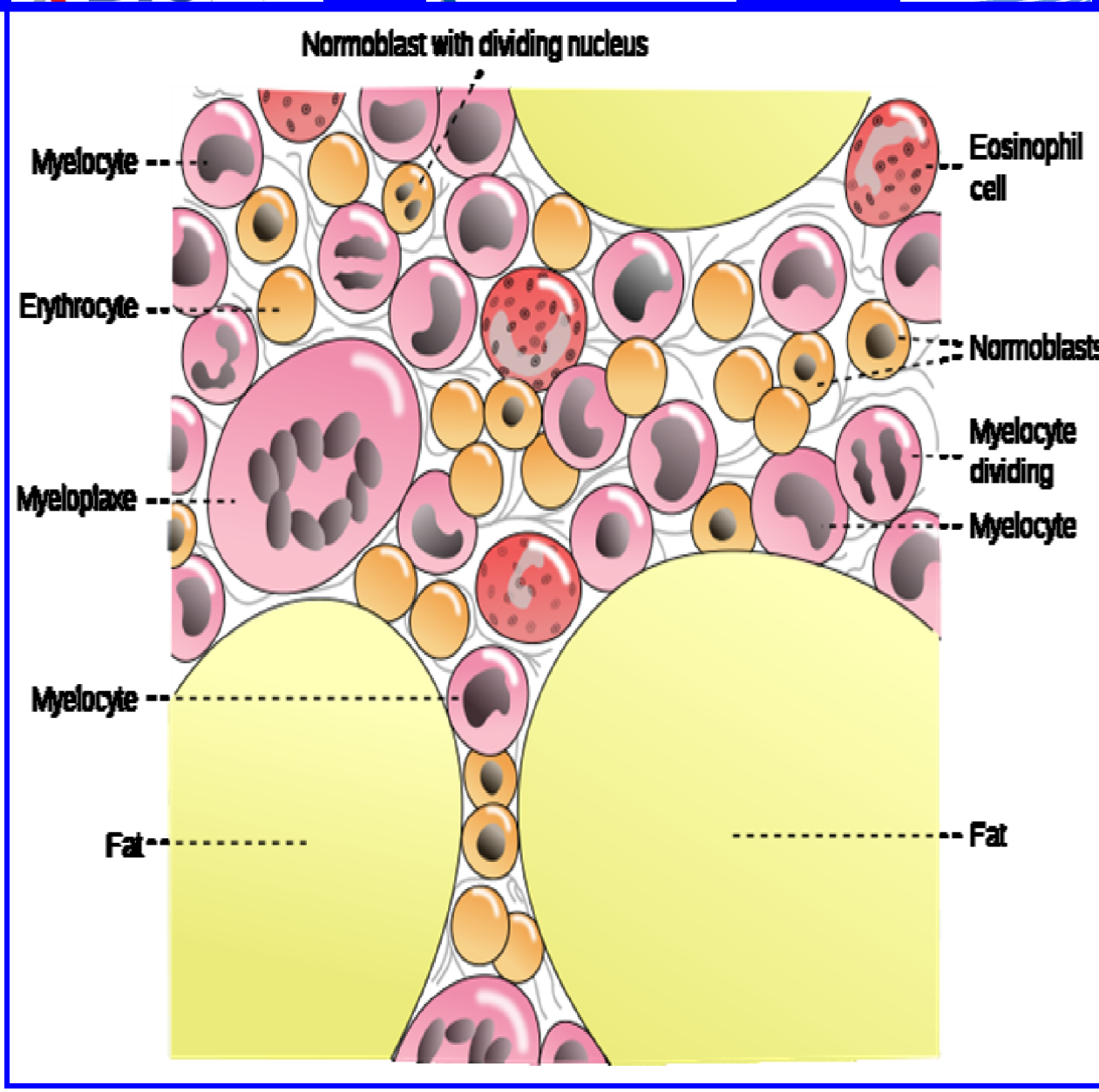
Guidelines for selection and HLA matching of related, adult unrelated donors and umbilical cord units for haematopoietic progenitor cell transplantation.



A collaborative publication by:

United Kingdom Paediatric Bone Marrow Transplant Group.

University of Leicester, 3rd Floor, Hearts of Oak House, 9 Princess Road West, Leicester LE1 6TH

http://www.cclg.org.uk

British Society for Histocompatibility and Immunogenetics

12 Coldbath Square, London, EC1R 5HL.

http://www.bshi.org.uk

The British Transplantation Society,

Chester House, 68 Chestergate, Macclesfield, Cheshire, SK11 6DY

secretariat@bts.org.uk

British Society for Blood and Marrow Transplantation

mail@bsbmt.org

Royal College of Pathologists

2 Carlton House Terrace, London,SW1Y 5AF

www.rcpath.org

Institute of Biomedical Science

12 Coldbath Square, London, EC1R 5HL.

www.ibms.org

Disclaimer:

These guidelines to best practice in stem cell donor selection will change with time. The guidelines present collective opinions from a numerous experts in the field and do not have the force of law. The guide is to be used as a tool towards best practice for progenitor cell donor selection and should be interpreted as thus. The guidelines present opinions and are subject to change and are not a treatment recommendation for an individual patient but as a general guide to best practice. The guidelines were prepared by a joint working party from the following professional societies:

- **United Kingdom Paediatric Bone Marrow Transplant Group.**
- **British Society for Histocompatibility and Immunogenetics**
- **British Society for Blood and Marrow Transplantation**
- **British Transplantation Society**
- **Royal College of Pathologists**
- **Institute of Biomedical Science**

The above named societies cannot attest to the accuracy, completeness or currency of the opinions contained herein and does not accept any responsibility or liability for any loss or damage caused to any practitioner or third party as a result of any reliance being placed on the guidelines or as a result of any inaccurate or misleading opinion contained in the guidelines.

Contents

Writing Committee:

The persons below, listed in alphabetic order have been asked to compile guidelines providing recommendations on current best practice for scientific professionals involved in the selection of haematopoietic progenitor cell donors. The guidelines are based upon peer reviewed studies and publications.

Dr David Briggs
Consultant Clinical Scientist
Histocompatibility and Immunogenetics Laboratory
NHS Blood and Transplant
Vincent Drive
Birmingham B15 2TT

Dr Ann Green
Consultant Clinical Scientist
British Bone Marrow Registry and Histocompatibility and Immunogenetics Laboratory
NHS Blood and Transplant
500 North Bristol Park
Filton
Bristol BS34 7QH

Dr Andrea Harmer
Consultant Clinical Scientist
Histocompatibility and Immunogenetics Laboratory
NHS Blood and Transplant
Longley Lane
Sheffield S5 7JN

Dr John Harvey
Principal Clinical Scientist
Histocompatibility and Immunogenetics Laboratory
NHS Blood and Transplant
500 North Bristol Park
Filton
Bristol BS34 7QH
Chairperson of writing committee

Dr Cristina Navarette
Consultant Clinical Scientist
NHSBT Head of H&I and BBMR
& Principal Investigator
Histocompatibility and Immunogenetics Laboratory
NHS Blood and Transplant
Colindale Avenue
London NW9 5BG

Dr Kay Poulton
Consultant Clinical Scientist
Histocompatibility and Immunogenetics Laboratory
Manchester Royal Infirmary
Oxford Road
Manchester M13 9WL

Clinical contributors:

Dr Jackie Cornish, OBE
Director of Paediatric Stem Cell Transplant
Head of Division
Division of Women's and Children's Services
Bristol Royal Hospital for Children
Bristol BS2 8BJ

Dr Brenda Gibson
Consultant Paediatric Haematologist
Royal Hospital for Sick Children
Dalnair Street
Glasgow, G3 8SJ

Prof. David Marks
Consultant Adult Haematologist
Avon haematology Unit
Bristol Oncology Centre
Horfield Road
Bristol BS2 8ED

Dr John Moppett
Consultant Paediatric Haematologist
Children's BMT Unit
Bristol Royal Hospital for Children
Bristol BS2 8BJ

Dr Steve Robinson
Consultant Adult Haematologist
Avon haematology Unit
Bristol Oncology Centre
Horfield Road
Bristol BS2 8ED

Dr Rod Skinner,
Consultant in Paediatric and Adolescent Oncology,
Children's BMT Unit,
Great North Childrens Hospital,
Royal Victoria Infirmary,
Newcastle upon Tyne.
NE1 4LP.
Principal Clinical Reviewer

Dr Mary Slatter
Associate specialist in Paediatric BMT
Children's BMT Unit
Great North Childrens Hospital,
Royal Victoria Infirmary,
Newcastle upon Tyne.
NE1 4LP

Dr Paul Veys
Consultant Paediatric Haematologist
Great Ormond Street Hospital for Children
Great Ormond Street
London WC1N 3JH

Dr Rob Wyn
Consultant Paediatric Haematologist
Royal Manchester Childrens Hospital
Hospital Road
Pendlebury
Manchester M27 1HA

Comments received from:

Prof. Nigel Russel and
Dr Bronwen Shaw
on behalf of
The British Society for Blood and Marrow Executive Committee

Dr. Ann-Margret Little
on behalf of
The Caledonian Histocompatibility and Immunogenetics Network (CHAIN)

Dr Vaughan Carter
Consultant Clinical Scientist
Histocompatibility and Immunogenetics Laboratory
NHS Blood and Transplant
Barrack Road
Newcastle NE2 4NQ

Dr. Brendan Clarke
Consultant Clinical Scientist
Histocompatibility and Immunogenetics Laboratory
St James Hospital
Leeds LS9 7TS

Prof. Dereck Middleton
Transplant Immunology,
Royal Liverpool University Hospital
Prescott Street,
Liverpool, L7 8XP

Dr. Katy Latham
On behalf of the:
Antony Nolan Laboratories
Fleet Road, London, NW3 2QG

Dr Craig Taylor
Consultant Clinical Scientist
Histocompatibility and Immunogenetics Laboratory
Adenbrookes Hospital
Hills Road
CB2 0QQ

Dr Leigh Keen
Senior Clinical Scientist
Histocompatibility and Immunogenetics Laboratory
NHS Blood and Transplant
Filton
Bristol BS34 7QH

Dr Martin Howell
Head of Department
Consultant Clinical Scientist
Histocompatibility and Immunogenetics Laboratory
NHS Blood and Transplant
Barrack Road
Newcastle NE2 4NQ

Mr. David Wilson
Principal Clinical Scientist
Immunology Department
Aberdeen Royal Infirmary
Aberdeen AB25 2ZN

Guidelines for selection and HLA matching of related, adult unrelated donors and umbilical cord units for haematopoietic progenitor cell transplantation.

1 Introduction

1.1 Overview

Strong evidence for significantly improved transplant outcome in unrelated donor haematopoietic progenitor cell transplants by matching for Human Leukocyte Antigens (HLA) using high resolution typing between patient and donor has been published over recent years (1-7). These retrospective studies involving multiple transplant centres, analysed the effect of HLA high resolution donor matching and mismatching on patient survival. Other studies have used an algorithm to define transplant pairs as “well matched, partially matched and mismatched” for HLA typing and retrospectively analysed transplant outcome showing an epoch dependent improvement in overall transplant survival (8).

From these and earlier studies the National Marrow Donor Program (NMDP, USA) issued HLA matching guidelines in 2003 (updated in 2008) of best practice for matched unrelated donor (MUD) progenitor cell transplants in adults (9). They describe guidelines for the optimal HLA match positively impacting post transplant survival in adult transplants(10). The core component of the NMDP guidelines for optimal transplant outcome requires a high resolution HLA-A, B, C and DRB1 loci matched unrelated donor to be used where a HLA matched sibling is not available. The guidelines further suggest that where a mismatch is unavoidable a single mismatched allele or antigen at HLA-A, -B, -C or -DRB1 donor should be selected. Similar guidelines are being used for HLA matching in a European prospective study (ALL-SCT-BFMi consortium) in progenitor cell transplants for children with Acute Lymphoblastic

Leukaemia (ALL) (11;12). The European study also includes HLA-DQB1 as locus for matching, the results of which are yet to be published.

1.2 Current status of unrelated donor HLA match criteria used in the UK

In 2009 a cross-sectional study of all Histocompatibility and Immunogenetics (H&I) laboratories in the UK and Ireland revealed that no uniform standards or guidelines are being applied for the HLA matching of unrelated recipient/donor pairs in progenitor cell transplantation (13). The survey shows that high resolution typing at HLA class-I and class-II for recipient/donor matching is performed in the selection of 40% of final transplant pairs in the UK and 100% in Ireland. The remaining 60% pairs are matched at the high resolution level for HLA class-II and low to intermediate resolution level for HLA class-I.

All laboratories surveyed matched at HLA-A, -B, and -DRB1 but there was no consensus on the use or need for matching at HLA-C, -DRB3, -DRB4, -DRB5, -DQB1 or -DPB1. Where a HLA matched donor was unavailable, 13 differing centre dependent criteria were in use to identify a suitable mismatched donor (table 1).

Table 1.
HLA mismatch criteria used where a fully matched donor is not an option

13 Algorithms submitted from 17 laboratories for the selection of a HLA mismatch donor when no HLA matched donor is available			
(A)>(B)>(DQB1)	(A)>(C)>(DQB1)	(C)>(A)>(B)	(C)>(A)>(DRB1)
(C)>(DQB1)>(DRB1)	(DPB1)>(DQB1)>(DRB1)	(DQB1)>(A)>(B)	(DQB1)>(A)
(DQB1)>(C)>(A)	(DPB1)>(DRB3,4,5)>(C)	(DQB1)>(A)>(DRB3,4,5)	(DPB1,DRB3,4,5)>(DQB1)>(C)
(C,DRB3,4,5,DQB1,DPB1)>(A)>(B,DRB1)			

Seventeen H&I laboratories returned thirteen differing algorithms (2009). All loci within brackets are given equal weighting and > equates to being preferred before the following loci. They are listed as (first preference) > (second preference) > (third preference).

This recent survey emphasised the wide variability in HLA matching and selection criteria used by progenitor cell transplant units in the UK.

1.3 The need for guidelines in the United Kingdom

The use of clinical guidelines founded on evidence-based medicine to set standards is an important aspect of clinical medicine and patient care. Guidelines for the allocation of solid organ donors have been published in the UK. No guidelines have been issued for related and unrelated allogeneic progenitor cell donor selection based on UK best practice.

Some publications provide recommendations in this setting but deal mostly with single disease aspects of transplantation or progenitor cell source (14;15). These guidelines are intended to be applicable to clinical practice in UK transplant centres.

1.4 Purpose of the guidelines

The aim of this document is to offer haematopoietic progenitor cell donor selection guidelines to clinical and biomedical scientists involved in donor selection for patients undergoing allogeneic progenitor cell transplantation. It is hoped that the guidelines may prove to be useful to other health care professionals in training. The guidelines highlight the most relevant HLA factors to consider in the rapid provision of the best matched related and unrelated adult volunteer progenitor cell donors or umbilical cord blood unit.

Clinical urgency as determined by the transplant team will remain the principal determinant that impacts the choices offered. It is hoped that the document will offer valuable guidance in a wide range of progenitor cell transplant scenarios.

Preparation of the guidelines

The guidelines were prepared by a working party of:

- **United Kingdom Paediatric Bone Marrow Transplant Group.**
- **British Society for Histocompatibility and Immunogenetics**
- **British Society for Blood and Marrow Transplantation**
- **British Transplantation Society**
- **Royal College of Pathologists**
- **Institute of Biomedical Science**

The guidelines are based on review and consensus literature up to July 2011. They shall be revised annually from 30th December 2012 onwards.

Recommendations strongly supported by current and historic literature or are mandatory for accreditation purposes, are bordered and highlighted thus.

Where a recommendation has more limited or contradicted support in the literature, the recommendation is bordered and highlighted thus.

2 HLA matching

2.1 Definitions of low, intermediate and high resolution, allelic and confirmed allele high resolution HLA typing:

The following definitions have been compiled by a joint working party from the following organisations: American Association of Blood Banks (AABB), American Society for Histocompatibility and Immunogenetics (ASHI), College of American Pathologists (CAP), European Federation for Immunogenetics (EFI), Foundation for the Accreditation of Cellular Therapy (FACT), National Marrow Donor Program (NMDP), World Marrow Donor Association (WMDA) (August 2010).

2.1.1 Low resolution (LR):

The DNA-based typing result is at the level of the digits comprising the first field in the DNA-based nomenclature. Examples include: A*01; A*02. The exception is B*15 in which low resolution is defined as a subset of alleles that might be considered as sharing a broad serologic type, either B15 or B70.

2.1.2 Intermediate resolution (IR):

Intermediate resolution is defined as a DNA-based typing result that includes a subset of alleles sharing the digits in the first field of their allele name and that excludes some alleles sharing those digits. Examples 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 with a group beginning with different digits but these alleles should be the exception i.e., the majority of the alleles should share the same first digits e.g., A*01:01 or A*01:02 or A*01:14 or A*36:04.

2.1.3 High resolution (HR):

A high resolution typing result is defined as a set of alleles that specify and encode the same protein sequence for the peptide binding region of a HLA molecule and that

excludes alleles that are not expressed as cell-surface proteins. Examples are typing with the following characteristics:

(a) Alleles within a P group designation e.g., A*02:01P, DPB1*04:02P. The 'P' group designation is assigned to alleles that encode for the same protein sequence in exon 2 and 3 for HLA class I and exon 2 for HLA class II.

(b) Alleles within a G group designation (e.g., A*02:01:01G, DRB1*12:01:01G) with the exception that it does not include non-expressed alleles with the same nucleotide sequence (e.g., A*02:01:01G without A*02:43N and A*02:83N). The 'G' designation is assigned to HLA alleles with the same nucleotide sequences across the exons encoding for peptide binding domains. A comprehensive explanation of P and G groups can be found at **http://hla.alleles.org/wmda/index.html**

2.1.4 **Allelic resolution (AR):**

The DNA-based typing result is consistent with a single allele as defined in a given version of the WHO HLA Nomenclature Report as described on the reference web site, http://hla.allele.org. An allele is defined as a unique nucleotide sequence for a gene as defined by the use of all of the digits in a current allele name. Examples include A*01:01:01:01; A*02:07.

2.1.5 **Confirmed allele high resolution (CAHR):**

A "confirmed" allele is one that has been identified in two or more unrelated individuals and is designated as "confirmed" in the IMGT/HLA database (**http://www.ebi.ac.uk/imgt/hla**). A confirmed allele high resolution typing result is defined as a set of alleles that specify and encode the same protein sequence for the peptide binding region of a HLA molecule, and exclude "confirmed" alleles that are not expressed as cell-surface proteins and include alternative genotypes with two

unconfirmed alleles that specify different protein sequences, when applicable. An example of confirmed allele high resolution typing is: A*02:01:01G in which the non-expressed alleles, A*02:43N and A*02:83N, are not excluded because they have not been identified in two or more unrelated individuals.

2.2 Stage of disease, time to transplant and HLA matching

One of the earliest steps in donor selection is to consider the disease and the potential progression of the patient. Patients with a slowly progressing disease such as myelodysplastic syndrome in low and intermediate-1 international prognostic score groups (IPSS), can have ample time to search for the best matched unrelated donor. In these cases delayed transplantation to source the best possible donor can maximise overall survival. However, in others cases such as patients with myelodysplasia in intermediate-2 and high risk IPSS, immediate transplantation is associated with maximal life expectancy (16).

This contrasts with acute leukaemia's where the patient's condition can rapidly deteriorate and a limited window of opportunity in terms of clinical remission may limit the time available for an unrelated donor search. The transplant physician must advise the H&I laboratory on the stage of the patient's disease (early, intermediate or advanced) giving an indication of clinical urgency. A patient progressing to advanced disease usually has a higher mortality risk from the disease than the added risk from a single HLA allele/antigen mismatch or alternative donor therapy such as umbilical cord blood (UCB) transplantation. The progress of the patients disease and the likelihood of finding a HLA matched donor will determine the choice of progenitor cell source selected for treatment (17).

The H&I specialist must advise on the likelihood of finding a high resolution matched donor within the time frame set by the transplant consultant. The likelihood of finding a high-resolution matched donor should be based upon the frequency of the HLA alleles and haplotypes in the population. Studies suggest that the ethnic origin of the patient and the likelihood of potential matches must be identified as early as possible (18-21).

Guidance and tools to assist in donor selection and allele frequencies are freely available at the following websites.

http://www.haplostats.org/home.do
http://www.marrow-donor.org/cgi-bin/DNA/dnatyp.pl
http://bioinformatics.nmdp.org/
http://www.marrow.org
http://www.bmdw.org
http://hla.alleles.org
http://www.ebi.ac.uk/imgt/hla/
www.allelefrequencies.net

Extended donor searches where uncommon HLA types are present usually fail to find a high resolution matched donor and sacrifice time to the progression of disease (17). Alternative progenitor cell sources or acceptance of a limited HLA mismatch with an unrelated panel donor should be explored early in the planning of the transplant where time to transplant is restricted by the progress of the patients disease. Transplant indications tables designed to advise transplanters, referring haematologists and recommended treatments may be found at the following website.

http://bsbmt.org/indications-table/

3 Recommendations for related progenitor cell donor selection.

3.1 HLA matched related donor

- **The patient, siblings and parents (where available) should be HLA-A, -B and -DRB1 typed at low resolution as a minimum requirement. Where consanguinity exists within family, additional relatives may also be typed as prospective donors.**
- **Where possible, familial haplotypes should be assigned to establish presumptive high resolution identity between donor and recipient. This typing should include the HLA -C and DQB1 loci.**
- **Where familial haplotypes cannot be established, recipient and selected donor should be high resolution typed at HLA-A, -B, -C, -DRB1 and -DQB1.**
- **Laboratories not able to perform HLA class-I or class-II high resolution typing must arrange for an EFI or ASHI accredited laboratory to perform these tests.**
- **Where there are ambiguities in an HLA type all alternative alleles must be listed in the typing report.**
- **For the patient and all selected matched siblings, a repeat sample for confirmatory HLA typing must be obtained and the patient and donor retyped.**
- **If a sibling is a HLA identical twin and is selected as a donor there is likely to be less of a graft versus leukaemic effect in the transplant.**

3.2 HLA mismatched related donors

If there are no HLA matched siblings, and the time to transplant is short, then mismatched related donors can be considered.

- **Where parents share a HLA haplotype or a parent is homozygous for HLA loci then a pheno-identical transplant can be considered. It is recommended that patient and donor are high resolution typed to determine the exact degree of HLA mismatch between donor and patient.**
- **Where a related donor differs from the patient for a single antigen (i.e. sibling with crossover) then a one antigen/allele mismatch transplant can be considered. The patient and donor should be high resolution typed to determine the full extent of mismatch.**
- **Parents and siblings sharing a single haplotype with the patient can be considered for a haploidentical related transplant.**
- **Where there is consanguinity within the family, a comprehensive family tree should be sketched and selected extended family testing can be considered where appropriate.**

4 Unrelated donor selection

4.1 Genetic factors impacting on the availability of a HLA matched unrelated progenitor cell donor.

The number of HLA-A, -B and -DRB1 low resolution matched donors available for a patient following a BMDW search often reflects the likelihood of finding a high resolution matched unrelated donor. It has been reported that Caucasoid patients have a 40-50% chance of having a high resolution matched donor at HLA-A, -B, -C, -DRB1 and -DQB1 (10/10 match) and that the

probability of finding a 10/10 high resolution match is highly predictable (22;23). The chance of a 10/10 match in other ethnic groupings is lower (24). The following factors should be considered when searching for a high resolution matched unrelated donor.

- Commonly found HLA-B and -C or HLA-DRB1 and -DQB1 associations have a positive impact on the likelihood of finding a donor.

- Uncommon haplotypes in which the allele of one locus is not in normal linkage disequilibrium with allele of neighbouring locus, such as uncommon HLA-B and -C or HLA-DRB1 and -DQB1 associations have a negative impact on likely donor availability.

- The frequencies of HLA-B and -C or HLA-DRB1 and -DQB1 associations in donor registries for differing ethnic groups are available for comparison with the HLA type of the patient (20;25;26) (see 2.2, tools to assist in donor selection).
- Two points that will negatively impact the availability of a matched donor are:
    - The presence of a patient allele with a frequency of <5% within the low resolution matched possible donors (e.g. B*44:05).
    - The presence of an allele in the patient that is a possible match for low resolution donor types where other alleles having frequencies >10% are the alternative possible mismatches (e.g. B*35, B*44, DRB1*04, DRB1*11, DRB1*13).
- The presence of alleles from the low resolution typing groups HLA-B51 and B18 or the presence of alleles HLA-B*27:05, B*44:02 and B*44:03 in the patient, have a raised risk of a HLA-C mismatch.
- Patients are less likely to find a matched donor from an ethnic group differing from their own (27)

- Patients with parents coming from differing ethnic groups (mixed race) have a raised risk of not finding a match.

4.2 Recommendations for unrelated donor selection

The benefits of high resolution matching for HLA decreases as the disease progresses from early to intermediate to advanced disease states. Disease progression and stated time to transplant must be considered when deciding if a search for a high resolution matched donor should be pursued, or an alternative more quickly available progenitor cell source such as progenitor cells from umbilical cord or HLA non-identical related transplant should be investigated (28). In Patients with unusual HLA types other progenitor cell sources should be considered early. EFI standards recommend minimum requirements for HLA typing in unrelated progenitor cell transplantation but do not specify a standard for matching; this is determined by local transplant policies.

NMDP guidelines for adults recommend that high resolution HLA matching for HLA-A, -B, -C and -DRB1 is used for the recipient and final progenitor cell transplant donor (high resolution typing defined in section 2.1.3 of this document)(10). Contemporaneous studies show this level of resolution and matching (8/8 match) to be the minimum level favourably influencing leukaemia free survival (LFS) in unrelated donor transplants (10).

Matching for HLA-DRB3, -DRB4, -DRB5 has not yet been shown to significantly improve LFS. A large study looked at HLA-DQB1 mismatches and showed an additive negative impact where there was an existing mismatch at HLA-A, -B, -C or -DRB1(4). Other studies indicate that HLA-DQ mismatches represent no added risk (3;29)

- **The recipient should be high resolution typed prior to submitting the donor type for an unrelated donor search.**
- **We recommend a 10/10 high resolution match at HLA-A, -B, -C,-DRB1 and DQB1 loci unrelated donor to be used where possible**
- **Where a 10/10 match is not possible a single mismatch at HLA-A, -B, -C, -DRB1 or DQB1 is acceptable (4).**
- **The transplant strategy must minimise the number of HLA allele mismatches between donor and recipient (4).**
- **Alternative progenitor cell sources should be considered early in the donor search where a patient is unlikely to have an HLA matched unrelated donor.**

Mismatches at HLA-DPB1 have been shown to offer a graft versus leukaemic advantage but also increased graft versus host disease and associated morbidity. A study has shown that there was no significant influence on overall survival associated with matching at this locus (30). Matching/mismatching at the DPB1 locus should be considered on an individual basis following the transplant physician's evaluation of the patients transplant related risks. Emerging literature refers to permissible and non-permissible mismatches for DPB1 (31;32).

5 HSC source

5.1 Peripheral Blood Progenitor cell (PBSC), Bone Marrow (BM) or Umbilical Cord Blood (UCB).

The choice of haematopoietic progenitor cell source is influenced by several factors; the urgency determined by the patient's condition, age, weight, disease status and the availability of a suitable HLA matched donor will determine the choice. Each progenitor cell source has distinct advantages and disadvantages requiring assessment in the best interest of the

patient. They differ in characteristics such as; cell dose, HLA matching requirement, risks of acute and chronic GvHD, time to engraftment and time to the availability of donor cells for transplantation.

In recent studies of paediatric transplants for acute leukaemia, UCB transplants with up to 2 HLA antigen mismatches had similar 5 year leukaemia free survival (LFS) as 8/8 high resolution matches at HLA-A, -B, -C or -DRB1 using unrelated BM and PBSC transplants. In adult BM and PBSC transplants, 8/8 high resolution matches at HLA-A, -B, -C or -DRB1 have lower transplant related mortality (TRM) and higher leukaemic free survival LFS than UCB transplants (33). UCB transplants with an adequate cell dose have a similar transplant outcome as single allele mismatched unrelated PBSC or BM transplant.

Where the maternal HLA type of a cord donation is known, non inherited maternal antigens (NIMA) when selected as a mismatch have been reported to reduce transplant related mortality and relapse rates (34).

It is recommended that UCB units are matched by high resolution typing for HLA-DRB1 and at intermediate resolution for HLA-A and B (14;35;36). Every effort should be made to minimise mismatching at these loci but where there is no choice a 5/6 or a 4/6 match may be acceptable. A 3/6 mismatch or worse is not recommended.

5.2 Progenitor cell source and engraftment

PBSC transplants offer the fastest neutrophil engraftment followed by BM with UCB transplants the slowest to engraft. Slow engraftment in UCB transplants is associated with higher post transplant morbidity. In a recent UCB transplant study HLA match and total nucleated cell dose were shown to independently influence the rate of neutrophil engraftment (37). In UCB transplants, engraftment can be enhanced by using more than one cord blood unit.

The use of more than one UCB unit is recommended for those patients for whom a single cord unit would offer an inadequate cell dose. In choosing a second UCB unit it is recommended that the UCB unit is HLA matched to the patient using criteria recommended in 5.1 (38)*.

**Note recent publication indicating that unit – unit matching is less important than total nucleated cells (TNC) in unit (39).*

5.3 UCB - HLA match, cell dose and engraftment

When selecting a cord blood unit, it is important to match the cell dose to the size of the patient being transplanted. A consensus has evolved that 2.5 x 10^7 nucleated cells per kilogram body weight is the minimum cell dose required to reliably achieve engraftment in unrelated cord blood transplants (40). UCB units have on average 1/10^{th} the number of lymphoid derived cells of an average BM collection(41). The cell dose from the cord blood unit and the degree of HLA matching affect engraftment. In general, the greater the level of mismatch the higher the cell dose needed for engraftment (35).

The University of Minnesota recommends the following adjustments to cell dose depending upon the HLA match category of the donor/recipient pair where matching is at high resolution level for HLA-DRB1 and low resolution level for HLA-A and B loci (41).

Recommendations on cell dose with HLA mismatch UBC transplants:

6/6 HLA match	**>3 x 10^7 nucleated cells per kilogram body weight**
5/6 HLA match	**>4 x 10^7 nucleated cells per kilogram body weight**
4/6 HLA match	**>5 x 10^7 nucleated cells per kilogram body weight**

5.4 CD34^{+ve} cells and engraftment

It is important to transplant sufficient CD34^{+ve} cells for engraftment to take place. PBSCs offer the highest yield of CD34^{+ve} cells, and Bone marrow harvests on very rare occasions fail to yield a sufficient CD34^{+ve} cell dose. However, with cord blood donations the CD34^{+ve} cell yield varies significantly form one unit to another. Total nucleated cell yield is more commonly used to assess UCB unit selection for transplantation.

Higher CD34^{+ve} cell doses (typically >2 x 10^6/kg body weight) result in better neutrophil and platelet engraftment and are associated with improved survival especially in unrelated transplants. CD34^{+ve} cell doses >8 x10^6 /kg of body weight are associated with increased chronic graft versus host disease where peripheral blood progenitor cells are used (42).

5.5 HLA antibodies and engraftment

The impact of HLA antibodies on engraftment has been unclear. Opinion was formed from contradictory case study reports in the literature with few cases available for analysis because of the matching criteria inherent in HLA matched related and unrelated donor transplants. The use of mismatched cord blood donors has led to more transplants being performed where the patient has

antibodies directed against HLA specificities present in the donor. Two recent studies indicate that the presence of HLA antibodies in the recipient becomes a significant risk factor of transplant non-engraftment where the HLA antigen specificity recognised by the antibody is present in the donor.

In a Japanese study of 374 cord blood transplants, 16.4% (41/250) of patients aged between 16 and 74 years transplanted for malignancies had HLA antibodies. Of those patients 8 had antibodies against cognate antigen present in the transplanted cord blood. Engraftment for patients with HLA antibodies but no cognate antigen in the transplanted cord was 93.6% with a median time to engraftment of 21 days. Where the cognate antigen was present in the donor engraftment fell to 58% (p=0.017), and a median time to engraftment of 46 days (43). A more recent NMDP study looking at failed BM transplants, found that the presence of recipient HLA antibodies reactive to donor HLA antigens (HLA-DSA) is associated with an increased risk of non-engraftment (OR 22.8, p=0.0002) (44). From these studies the following can be considered best practice in HLA mismatched progenitor cell transplants. HLA-DSA in the recipient should be considered as a potential significant risk factor for non-engraftment.

- **In certain patients especially those with multiple risks of post transplant graft failure, the testing for HLA antibodies should be considered.***
- **In selecting HLA mismatched donors (CB, PBSC or BM) the transplant team must be made aware of any HLA antibody incompatibility detected.**

** Further studies in this area are needed to confirm the significance of donor specific HLA antibodies and non-engraftment.*

Some German, Italien and Israeli transplant centres have reported that progenitor cell dose (mega dose) in mismatch transplants can overcome immune barriers to transplantation(45;46). The effectiveness of this strategy in the presence of HLA-DSA in the recipient is unknown and is not common practice in the United Kingdom.

5.6 Acute graft versus host disease (aGvHD) and HLA mismatching

Acute GvHD is a major hazard in progenitor cell transplantation and a significant cause of death. HLA mismatches between donor and recipient are reported as major risk factors for aGvHD (47). Other possible risk factors include sero-positivity for herpes viruses and female donor to male recipient transplants (48).

Lymphoid cells from cord blood have decreased reactivity and are described as being naive and immature cells. The aGvHD risks associated with umbilical cord blood transplants are lower than those of PBSC and BM (37;49;50).Grade I and II aGvHD has been reported as a favourable factor contributing to disease free survival in malignancies(51;52).

5.7 Chronic graft versus host disease (cGvHD) and HLA mismatching

Chronic GvHD is a more diverse syndrome than aGvHD and the grading of this disease is more complex (53-55). The recognised independent variables seen to influence susceptibility to cGvHD are HLA mismatch, progenitor cell source, prior aGvHD and increasing age of patient. In homogeneous ethnic populations the sharing of minor histocompatibility antigens is reported to lower the incidence of cGvHD(56).

Table2. Selection criteria differences to be considered between BM, PBSC and CB progenitor cell sources.

Progenitor cell selection criteria	BM	PBSC	UCB
HLA matching	Minimum 8/10 HLA-A,B,C,DRB1,DQB1	Minimum 8/10 HLA-A,B,C,DRB1,DQB1	Minimum 4/6 HLA-A,B,DRB1
Average time to neutrophil engraftment	15-23 days	12-19 days	22-32 days
Time to identify, HLA retype and harvest donor cells	ø2-4 months	ø2-4 months	ø2 month
Availability of second donation and donor lymphocyte infusions	Yes	Yes	No

ø*British Bone Marrow Registry & NHSBT cord bank, 2011*

6 Non-HLA factors to be considered for selection

6.1 Cytomegalovirus (CMV)

Even with recent improvements in anti-viral and GvHD prophylactic therapies, CMV remains a major cause of morbidity and mortality in allogeneic SCT.

CMV seropositive patients having CMV seropositive donors have been shown to have better survival and reduced TRM than seropositive patients receiving seronegative progenitor cell donations (57). Published data in North America (58) indicates that seronegative patients with seropositive donors develop primary CMV infection in 30% of cases and have an increased mortality (59;60). The patients in these studies were supported post transplant with leukodepleted or CMV seronegative blood products.

It is recommended that CMV seropositive patients receive seropositive donors and seronegative patients receive seronegative donors wherever possible. Strategies should be adopted to avoid blood product-associated CMV infections in seronegative recipients by either leukodepleted products or CMV negative products.

6.2 ABO blood group

ABO incompatibility between patient and donor is a common feature of progenitor cell transplantation and does not constitute a major contra indication to donor selection. However strategies designed to reduce transplant-related toxicity such as low intensity conditioning and graft versus host prophylactics is associated with extended host isohaemaglutinin production. This can result in delayed donor erythropoiesis post transplant. Patients with pre-existing erythropoiesis problems have been shown to require prolonged red blood cell transfusion therapy post transplant.

These complications can be reduced where major ABO mismatches are avoided in donor selection (61).

It is recommended that where a patient has multiple HLA and CMV matched donors, major ABO incompatibilities should be avoided where possible.

6.3 Gender

For most conditions treated by SCT it has been reported that a male donor has a positive effect on long term survival regardless of the gender of the recipient (62;63). Other large multi-transplant centre studies found no such effect (4). Female recipients are at a greater risk of experiencing other complications such as thrombotic thrombocytopenia purpura post transplant, regardless of donor gender (64).

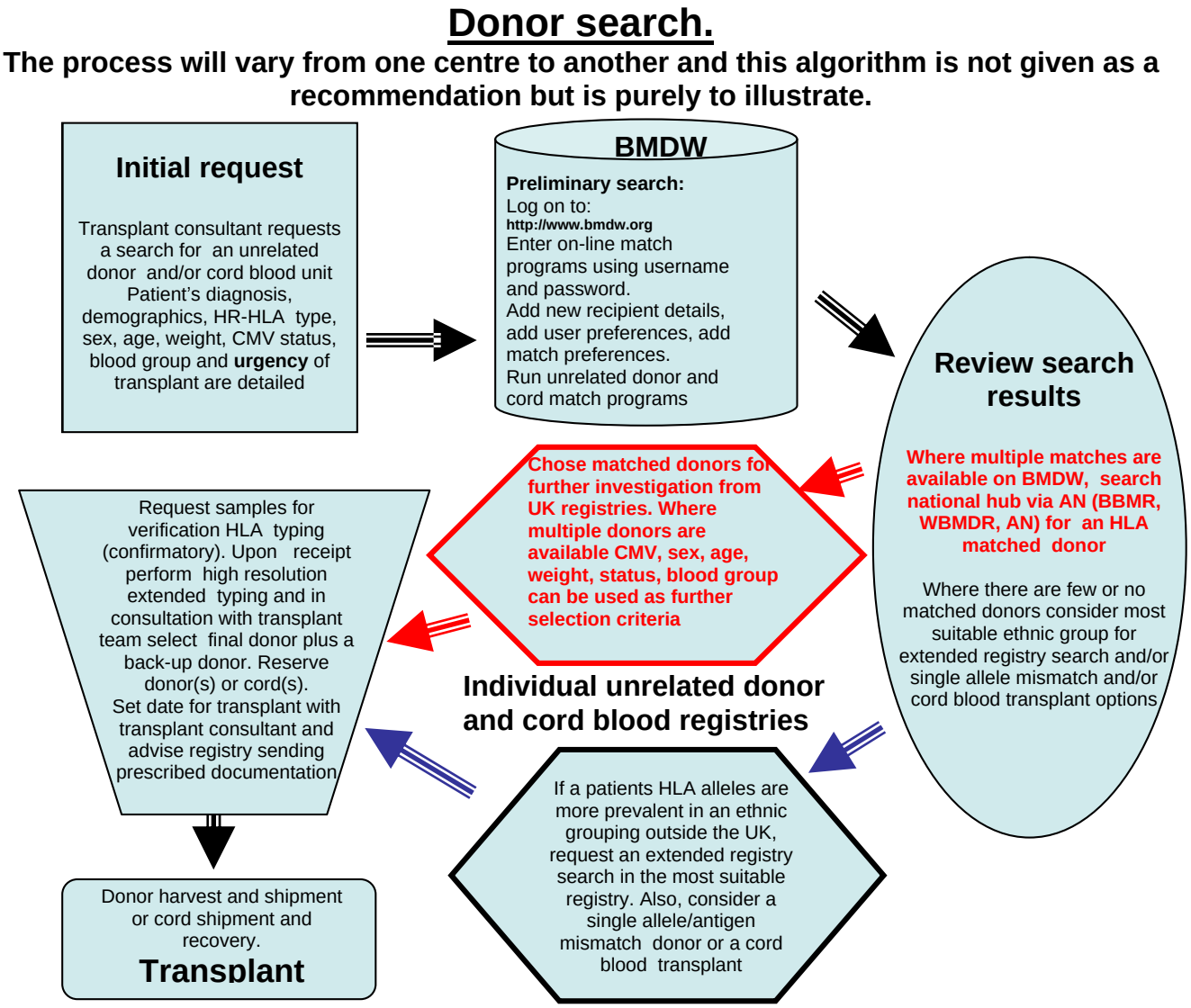
6.4 Donor Age

In a 2001, NMDP study of 6978 unrelated donor transplants performed from 1987 to 1999 the age of the donor at time of transplant was associated with lower levels of aGvHD and cGvHD and improved OS. This study was prior to the introduction of high resolution HLA matching for class I. A further study in children lacking a matched sibling donor, found that young donor age was the most important factor that has a significant effect on better survival from among several other factors, including CMV sero-status, gender and ABO (15). However a large NMDP study of 3857 transplants where high resolution matching was included was unable to confirm this donor age effect (4).

It is recommended for most patients undergoing SCT that a younger donor is the preferred option.

7 Algorithm for a donor search

The following algorithm outlines a generic process for identifying HLA matched progenitor cell donors or umbilical cord units for a UK patient. The algorithm is not meant to represent universal practice as individual transplant units and/or HLA laboratories must have their own operating procedures outlining each step of the process and must be a registered user with Bone Marrow Donors Worldwide. A comprehensive user guide is available from http://www.bmdw.org and further advice is available from individual registries.



8 H&I Laboratory - Operational Recommendations

- **The H&I laboratory must be directed by a consultant or equivalent trained and qualified in Histocompatibility and Immunogenetics.**
- **There must be close liaison between the H&I laboratory and the transplant unit.**
- **There must be close liaison with the national hub for donor registries managed through the Anthony Nolan.**
- **The H&I laboratory must provide a named person who is responsible for the co-ordination of the search progress with cover support for absences.**
- **Each case must be reviewed on an individual basis establishing urgency and suitability of the donor search strategy.**
- **The laboratory must have a written strategy designed to minimise the time from unrelated donor search to final donor selection.**
- **The laboratory must be accredited with the European Federation for Immunogenetics or the American Society for Histocompatibility and Immunogenetics to meet the transplant unit JACIE requirements.**

Reference List

1. Petersdorf EW. HLA matching in allogeneic stem cell transplantation. Curr.Opin.Hematol. 2004;11(6):386-91.

2. Petersdorf EW, Anasetti C, Martin PJ, Gooley T, Radich J, Malkki M et al. Limits of HLA mismatching in unrelated hematopoietic cell transplantation. Blood 2004;104(9):2976-80.

3. Flomenberg N, Baxter-Lowe LA, Confer D, Fernandez-Vina M, Filipovich A, Horowitz M et al. Impact of HLA class I and class II high-resolution matching on outcomes of unrelated donor bone marrow transplantation: HLA-C mismatching is associated with a strong adverse effect on transplantation outcome. Blood 2004;104(7):1923-30.

4. Lee SJ, Klein J, Haagenson M, Baxter-Lowe LA, Confer DL, Eapen M et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. Blood 2007;110(13):4576-83.

5. Petersdorf EW, Gooley T, Malkki M, Horowitz M. Clinical significance of donor-recipient HLA matching on survival after myeloablative hematopoietic cell transplantation from unrelated donors. Tissue Antigens 2007;69 Suppl 1:25-30.

6. Petersdorf E, Bardy P, Cambon-Thomsen A, Goulmy E, Hansen J, Schwarer A et al. 14thInternational HLA and Immunogenetics Workshop: report on hematopoietic cell transplantation. Tissue Antigens 2007;69 Suppl 1:17-24.

7. Petersdorf EW. Optimal HLA matching in hematopoietic cell transplantation. Curr.Opin.Immunol. 2008;20(5):588-93.

8. Macmillan ML, Davies SM, Nelson GO, Chitphakdithai P, Confer DL, King RJ et al. Twenty years of unrelated donor bone marrow transplantation for pediatric acute leukemia facilitated by the National Marrow Donor Program. Biol.Blood Marrow Transplant. 2008;14(9 Suppl):16-22.

9. Hurley CK, Baxter Lowe LA, Logan B, Karanes C, Anasetti C, Weisdorf D et al. National Marrow Donor Program HLA-matching guidelines for unrelated marrow transplants. Biol.Blood Marrow Transplant. 2003;9(10):610-5.

10. Bray RA, Hurley CK, Kamani NR, Woolfrey A, Muller C, Spellman S et al. National marrow donor program HLA matching guidelines for unrelated adult donor hematopoietic cell transplants. Biol.Blood Marrow Transplant. 2008;14(9 Suppl):45-53.

11. Peters C, Schrauder A, Schrappe M, von Stackelberg A, Stary J, Yaniv I et al. Allogeneic haematopoietic stem cell transplantation in children with acute lymphoblastic leukaemia: the BFM/IBFM/EBMT concepts. Bone Marrow Transplant. 2005;35 Suppl 1:S9-11.

12. Schrauder A, von Stackelberg A, Schrappe M, Cornish J, Peters C. Allogeneic hematopoietic SCT in children with ALL: current concepts of ongoing prospective SCT trials. Bone Marrow Transplant. 2008;41 Suppl 2:S71-S74.

13. Harvey J, Green A. Survey of human leukocyte antigen matching criteria used in donor selection for haematopoietic stem cell transplantation in the United Kingdom and Ireland.(Abstract). Hum.Immunol. 2009;70 suplement 1:S97.

14. Rocha V, Locatelli F. Searching for alternative hematopoietic stem cell donors for pediatric patients. Bone Marrow Transplant. 2008;41(2):207-14.

15. Lanino E, Sacchi N, Peters C, Giardino S, Rocha V, Dini G. Strategies of the donor search for children with second CR ALL lacking a matched sibling donor. Bone Marrow Transplant. 2008;41 Suppl 2:S75-S79.

16. Cutler CS, Lee SJ, Greenberg P, Deeg HJ, Perez WS, Anasetti C et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome. Blood 2004;104(2):579-85.

17. Weisdorf D. Should all unrelated donors for transplantation be matched? Best.Pract.Res.Clin.Haematol. 2008;21(1):79-83.

18. Hurley CK, Setterholm M, Lau M, Pollack MS, Noreen H, Howard A et al. Hematopoietic stem cell donor registry strategies for assigning search determinants and matching relationships. Bone Marrow Transplant. 2004;33(4):443-50.

19. Kollman C, Maiers M, Gragert L, Muller C, Setterholm M, Oudshoorn M et al. Estimation of HLA-A, -B, -DRB1 haplotype frequencies using mixed resolution data from a National Registry with selective retyping of volunteers. Hum.Immunol. 2007;68(12):950-8.

20. Cano P, Klitz W, Mack SJ, Maiers M, Marsh SG, Noreen H et al. Common and well-documented HLA alleles: report of the Ad-Hoc committee of the american society for histocompatiblity and immunogenetics. Hum.Immunol. 2007;68(5):392-417.

21. Spellman S, Setterholm M, Maiers M, Noreen H, Oudshoorn M, Fernandez-Vina M et al. Advances in the selection of HLA-compatible donors: refinements in HLA typing and matching over the first 20 years of the National Marrow Donor Program Registry. Biol.Blood Marrow Transplant. 2008;14(9 Suppl):37-44.

22. Tiercy JM, Bujan-Lose M, Chapuis B, Gratwohl A, Gmur J, Seger R et al. Bone marrow transplantation with unrelated donors: what is the probability of identifying an HLA-A/B/Cw/DRB1/B3/B5/DQB1-matched donor? Bone Marrow Transplant. 2000;26(4):437-41.

23. Tiercy JM, Nicoloso G, Passweg J, Schanz U, Seger R, Chalandon Y et al. The probability of identifying a 10/10 HLA allele-matched unrelated donor is highly predictable. Bone Marrow Transplant. 2007;40(6):515-22.

24. Schmidt AH, Solloch UV, Baier D, Yazici B, Ozcan M, Stahr A et al. Criteria for initiation and evaluation of minority donor programs and application to the example of donors of Turkish descent in Germany. Bone Marrow Transplant. 2009;44(7):405-12.

25. Maiers M, Gragert L, Klitz W. High-resolution HLA alleles and haplotypes in the United States population. Hum.Immunol. 2007;68(9):779-88.

26. Kollman C, Maiers M, Gragert L, Muller C, Setterholm M, Oudshoorn M et al. Estimation of HLA-A, -B, -DRB1 haplotype frequencies using mixed resolution data from a National Registry with selective retyping of volunteers. Hum.Immunol. 2007;68(12):950-8.

27. Schmidt AH, Solloch UV, Baier D, Yazici B, Ozcan M, Stahr A et al. Criteria for initiation and evaluation of minority donor programs and application to the example of donors of Turkish descent in Germany. Bone Marrow Transplant. 2009;44(7):405-12.

28. Bachanova V, Weisdorf D. Unrelated donor allogeneic transplantation for adult acute lymphoblastic leukemia: a review. Bone Marrow Transplant. 2008;41(5):455-64.

29. Woolfrey A, Klein J, Haagenson M, Spellman S, Petersdorf E, Oudshoorn M et al. HLA-C Antigen mismatch is associated with worse outcome in unrelated donor peripheral blood stem cell transplantation. Biol.Blood Marrow Transplant. 2010;17(6):885-92.

30. Shaw BE, Gooley TA, Malkki M, Madrigal JA, Begovich AB, Horowitz MM et al. The importance of HLA-DPB1 in unrelated donor hematopoietic cell transplantation. Blood 2007;110(13):4560-6.

31. Crocchiolo R, Zino E, Vago L, Oneto R, Bruno B, Pollichieni S et al. Nonpermissive HLA-DPB1 disparity is a significant independent risk factor for mortality after unrelated hematopoietic stem cell transplantation. Blood 2009;114(7):1437-44.

32. Fleischhauer K, Shaw BE, Gooley T, Malkki M, Bardy P, Bignon JD et al. Effect of T-cell-epitope matching at HLA-DPB1 in recipients of unrelated-donor haemopoietic-cell transplantation:a retrospective study. Lancet Oncol. 12 A.D.;13(4):366-74.

33. Eapen M, Rubinstein P, Zhang MJ, Stevens C, Kurtzberg J, Scaradavou A et al. Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: a comparison study. Lancet 2007;369(9577):1947-54.

34. van Rood JJ, Stevens CE, Smits J, Carrier C, Carpenter C, Scaradavou A. Reexposure of cord blood to noninherited maternal HLA antigens improves transplant outcome in hematological malignancies Proc.Natl.Acad.Sci.U.S.A 2009;106(47):19952-7.

35. Hurley CK, Wagner JE, Setterholm MI, Confer DL. Advances in HLA: practical implications for selecting adult donors and cord blood units. Biol.Blood Marrow Transplant. 2006;12(1 Suppl 1):28-33.

36. Gluckman E, Koegler G, Rocha V. Human leukocyte antigen matching in cord blood transplantation. Semin.Hematol. 2005;42(2):85-90.

37. Kurtzberg J, Prasad VK, Carter SL, Wagner JE, Baxter-Lowe LA, Wall D et al. Results of the Cord Blood Transplantation Study (COBLT): Clinical outcomes of unrelated donor umbilical cord blood transplantation in pediatric patients with hematologic malignancies. Blood 2008;112(10):4318-27.

38. Barker JN, Weisdorf DJ, DeFor TE, Blazar BR, McGlave PB, Miller JS et al. Transplantation of 2 partially HLA-matched umbilical cord blood units to enhance engraftment in adults with hematologic malignancy. Blood 2005;105(3):1343-7.

39. Barker JN, Byam C, Scaradavou A. How I treat: the selection and acquisition of unrelated cord blood grafts Blood 2011;117(8):2332-9.

40. Laughlin MJ, Eapen M, Rubinstein P, Wagner JE, Zhang MJ, Champlin RE et al. Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia. N.Engl.J.Med. 2004;351(22):2265-75.

41. Gluckman E. Cord blood transplantation. Biol.Blood Marrow Transplant. 2006;12(8):808-12.

42. Heimfeld S. HLA-identical stem cell transplantation: is there an optimal CD34 cell dose? Bone Marrow Transplant. 2003;31(10):839-45.

43. Takanashi, M., Fujiwara, K., Tanaka, H., Satake, M., and Nakajima, K. The impact of HLA antibodies on engraftment of unrelated cord blood transplants. Transfusion 48, 791-792. 1-4-2008.

44. Spellman S, Bray R, Rosen-Bronson S, Haagenson M, Klein J, Flesch S et al. The detection of donor-directed, HLA-specific alloantibodies in recipients of unrelated hematopoietic cell transplantation is predictive of graft failure. Blood 2010.

45. Gur H, Krauthgamer R, Berrebi A, Klein T, Nagler A, Tabilio A et al. Tolerance induction by megadose hematopoietic progenitor cells: expansion of veto cells by short-term culture of purified human CD34(+) cells. Blood 2002;99(11):4174-81.

46. Handgretinger R, Klingebiel T, Lang P, Schumm M, Neu S, Geiselhart A et al. Megadose transplantation of purified peripheral blood CD34(+) progenitor cells from HLA-mismatched parental donors in children. Bone Marrow Transplant. 2001;27(8):777-83.

47. Bacigalupo A, Sormani MP, Lamparelli T, Gualandi F, Occhini D, Bregante S et al. Reducing transplant-related mortality after allogeneic hematopoietic stem cell transplantation. Haematologica 2004;89(10):1238-47.

48. Ringden O, Pavletic SZ, Anasetti C, Barrett AJ, Wang T, Wang D et al. The graft-versus-leukemia effect using matched unrelated donors is not superior to HLA-identical siblings for hematopoietic stem cell transplantation. Blood 2009;113(13):3110-8.

49. Smith AR, Wagner JE. Alternative haematopoietic stem cell sources for transplantation: place of umbilical cord blood. Br.J.Haematol. 2009;147(2):246-61.

50. Bacigalupo A, Frassoni F, Van Lint MT. Bone marrow or peripheral blood as a source of stem cells for allogeneic transplantation. Haematologica 2002;87(8 Suppl):4-8.

51. Chim CS, Lie AK, Liang R, Au WY, Kwong YL. Long-term results of allogeneic bone marrow transplantation for 108 adult patients with acute lymphoblastic leukemia: favorable outcome with BMT at first remission and HLA-matched unrelated donor. Bone Marrow Transplant. 2007;40(4):339-47.

52. Esperou H, Boiron JM, Cayuela JM, Blanchet O, Kuentz M, Jouet JP et al. A potential graft-versus-leukemia effect after allogeneic hematopoietic stem cell transplantation for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: results from the French Bone Marrow Transplantation Society. Bone Marrow Transplant. 2003;31(10):909-18.

53. Akpek G, Zahurak ML, Piantadosi S, Margolis J, Doherty J, Davidson R et al. Development of a prognostic model for grading chronic graft-versus-host disease. Blood 2001;97(5):1219-26.

54. Akpek G, Lee SJ, Flowers ME, Pavletic SZ, Arora M, Lee S et al. Performance of a new clinical grading system for chronic graft-versus-host disease: a multicenter study. Blood 2003;102(3):802-9.

55. Horwitz ME, Sullivan KM. Chronic graft-versus-host disease. Blood Rev. 2006;20(1):15-27.

56. Remberger M, Aschan J, Lonnqvist B, Carlens S, Gustafsson B, Hentschke P et al. An ethnic role for chronic, but not acute, graft-versus-host disease after HLA-identical sibling stem cell transplantation. Transplant.Proc. 2001;33(1-2):1769-70.

57. Ljungman P, Brand R, Einsele H, Frassoni F, Niederwieser D, Cordonnier C. Donor CMVserological status `and outcome of CMV seropositive recipients after unrelated donor stem cell transplantation: an EBMT megafile analysis. Blood 2003;102:4255-60.

58. Nichols WG, Corey L, Gooley T, Davis C, Boechh M. High risk of death due to bacterial and fungal infection among cytomegalovirus (CMV)-seronegative recipients of stem cell donors from seropositive donors; evidence for indirect effects of primary CMV infection. J.Infec.Dis. 2002;185:273-82.

59. Boeckh M, Nichols WG, Papanicolaou G, Rubin R, Wingard JR, Zaia J. Cytomegalovirus in hematopoietic stem cell transplant recipients: Current status, known challenges, and future strategies. Biol.Blood Marrow Transplant. 2003;9(9):543-58.

60. Ljungman P, Hakki M, Boeckh M. Cytomegalovirus in hematopoietic stem cell transplant recipients Infect.Dis.Clin.North Am. 2010;24(2):319-37.

61. Bolan CD, Leitman SF, Griffith LM, Wesley RA, Procter JL, Stroncek DF et al. Delayed donor red cell chimerism and pure red cell aplasia following major ABO-incompatible nonmyeloablative hematopoietic stem cell transplantation Blood 2001;98(6):1687-94.

62. Pond GR, Lipton JH, Messner HA. Long-term survival after blood and marrow transplantation: comparison with an age- and gender-matched normative population Biol.Blood Marrow Transplant. 2006;12(4):422-9.

63. Gustafsson JA, Remberger M, Ringden O, Winiarski J. Risk factors in pediatric stem cell transplantation for leukemia. Pediatr.Transplant. 2004;8(5):464-74.

64. Fuge R, Bird JM, Fraser A, Hart D, Hunt L, Cornish JM et al. The clinical features, risk factors and outcome of thrombotic thrombocytopenic purpura occurring after bone marrow transplantation Br.J.Haematol. 2001;113(1):58-64.